ISSN: 2520-7695 (Print) and XXXX-XXXX (Online)
Medical and Health Sciences Research Journal
Med. Health Sci. Res. J., Jan-Apr 2017, 1(1): 01-06
Journal Homepage: http://www.mhsrjournal.com/
http://www.wollegajournals.com/

Original Research

Periportal fibrosis in *Schistosoma mansoni* Mono and Malaria- *Schistosoma* Co-infected Individuals in Finchaa Sugar Estate, Western Ethiopia

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Abstract

In Ethiopia where malaria parasite and *Schistosoma mansoni* infections are co-endemic, the general population is quite vulnerable both to malaria and *Schistosoma mansoni* infections singly or concomitantly. However, data on PPF due to single and co-infections are lacking. The aim of this study was to assess the status of PPF in *S. mansoni* mono infected and malaria-*S. mansoni* co-infected individuals. A community based cross sectional study was conducted in Finchaa Sugar Estate, western Ethiopia. Schistosomal periportal and portal liver fibrosis were determined by ultrsonography. SPSS statistical software version 20 was used and *P*-value <0.05 was reported as statistically significant. The findings of this study showed that *P. falciparum* and *S. mansoni* co-infection reciprocally increase the degree of PPF. The study has provided an additional sonographic data on the reciprocal effects of *P. falciparum* and *S. mansoni* co-infection, and could serve as a guide in designing, developing and implementing intervention strategies to mitigate co-morbidity due to co-infection among the high risk groups in Ethiopia and other endemic areas of the world.

Article Information

Article History:
Received : 02-02-2017
Revised : 29-03-2017
Accepted : 16-04-2017

Keywords:
Co-infections
Co-morbidity
Periportal fibrosis
Plasmodium falciparum
Plasmodium vivax
Finchaa Sugar Estate

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INTRODUCTION

Malaria, schistosomiasis and intestinal helminth infections are causes of high morbidity in most tropical parts of the world (Mazigo *et al*., 2010). Schistosoma infection is one of the most important causes of non-cirrhotic portal hypertension in Latin America, Africa, and Asia (Bodh and Chawla, 2014).The most prominent feature of liver pathology in schistosomiasis is represented by a process of portal fibrosis that extends from the smallest to the largest portal spaces. It forms a typical gross finding that can be appreciated not only at the surface of the liver at autopsy but also from images obtained by ultrasound or magnetic-resonance techniques (Homeida *et al*., 1988; Franke *et al*., 1991).Extensive portal fibrosis is associated with a schistosome infection with a heavy worm burden, as it is the presence of numerous schistosome eggs that causes a sufficient peripheral block of small portal vessels. The possibility of antagonistic or synergistic interactions between parasites appears to be the mechanism in play (Whittle *et al*., 1969; Sokhna *et al*., 2004; Booth *et al*., 2004c; Faye *et al*., 2008; Wilson *et al*., 2009).

Hepatosplenomegaly can be caused by long-term exposure to malaria, or by schistosomiasis mansoni, and it is exacerbated when these two occur together (Wilson *et al*., 2009). Chronic co-exposure to the two parasites can result in both greater prevalence of hepatosplenomegaly (Whittle *et al*., 1969). A retrospective study conducted in Kenya by Booth *et al*. (2004b) and a prospective study conducted in northern Senegal by Sokhna *et al*. (2004) suggested that malaria- *Schistosoma mansoni* co-infection increased splenomegaly in 6-16 years age group. In terms of pathological outcomes, co-infections with malaria and schistosome parasites may also have synergistic effects on the organ pathology and increased hepatosplenomegaly has been reported in intestinal schistosomiasis malaria co-infected individuals (Booth *et al*., 2004c). The outcome of treating cases of hepatosplenomegaly with praziquantel depended strongly on their level of exposure to malaria infection and exposure to malaria infection may be a significant factor affecting the outcome of praziquantel treatment to reduce the level of hepatosplenic morbidity (Booth *et al*., 2004c). This study assessed Periportal fibrosis (Grade C) and Portal fibrosis (Grade D).

MATERIALS AND METHODS

Study Area

This study was undertaken in Finchaa Sugar Estate which is located in Finchaa Valley, Oromia Regional state, western Ethiopia (Figure 1).The area is about 325 km west of Addis Ababa and is situated between 9^0 30'N to 9^0

60' N latitudes and 37^0 10' to 37^0 30' E longitudes at an altitude of about 1,350-1,600 m above sea level with the average annual rainfall of 1,300 mm. The Sugar Estate is cultivating more than 18,000 hectares of irrigated land using sprinkle irrigation system with a production of 10,000 kg of sugar per day. The Sugar Estate has about seven camps, with one elementary school, one community health agent and one health center in Agemsa village.

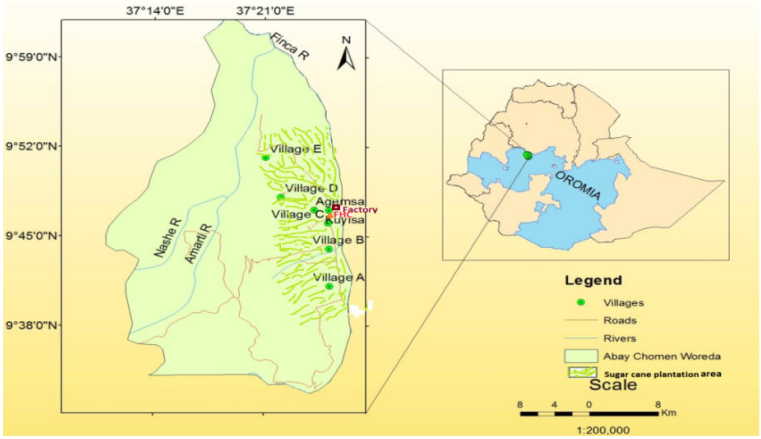

Figure 1: Sketch-map of the study area -Finchaa Sugar Estate, western Ethiopia (Source: Garmin 72 GPS)

Study Participants

The study populations were residents of the three purposively selected villages, namely Camp 7, Kuyissa and Agemsa. A study participant who fulfilled the inclusion criteria were selected from the community lists using stratified random sampling methods from the three villages after informed consent/assent.

Ultrasound Examination

Ultrasonographic assessments were performed to detect pathological changes associated with *Schistosoma mansoni* and malaria-*Schistosoma mansoni* co-infection using a EUB 405 portable ultrasound apparatus (Hitachi Tokyo, Japan) fitted with 3.5-MHz convex abdominal probe.

Treatment

All participants who were positive for malaria were treated with anti-malarial drugs. Also individuals found positive for *S. mansoni* and STH infections were treated with a single dose of praziquantel 40 mg/kg and mebendazole 500 mg, respectively. In addition, based on ultrasound determinations, patients who had definite schistosomal liver periportal fibrosis were treated with praziquantel every four weeks for 4-6 months. All treatments were given free of charge under the supervision of physicians at the health center according to the national treatment protocols (FMoH, 2004).

Data Analysis

Data were entered into a computer and validation was performed in Microsoft Excel 2007 spreadsheets, and transferred into SPSS version 20.0 software for statistical analysis. Descriptive statistics was used to provide a clear picture of background variables. Intensity of *S.mansoni* infection (Epg) and malaria parasite (parasites/µ) were expressed as means among study participants. All graphs were drawn using MS-Excel and all box-plots were drawn using SPSS version 20.0. *P*-value <0.05 was reported as statistically significant. To determine ultrasonographic measurements, ultrasound image patterns suggestive of periportal fibrosis were compared with standard images and the corresponding image pattern scores were recorded using the WHO-Niamey protocol (Richter *et al.,* 2000). All examinations were performed by the same radiographer who was blinded to the schistosome infection status of the individuals.

Ethical Considerations

The study was approved by the Research Ethics Review Committee of Collage of Natural Sciences, Addis Ababa University and by the National Research Ethics Review Committee. To participate in the research project and written consent/assent was obtained from the parents/guardians on the behalf of all child participants (under 18 years of age).

RESULTS

Socio-demographic Characteristics

A total of 810 study participants (males 51.23% and females 48.77%) were included in the study. Their mean age, hemoglobin, *S. mansoni* Epg and malaria parasites/µL were 23, 13.84g/dL, 241 and 574, respectively.

Among the 810 study participants, 452 (55.81 %) harbored at least one parasitic infection and 358 (44.20%) had none of the studied parasitic infections. Among mono-infections, the most prevalent parasitic infection was *S. mansoni* 14.44%, followed by malaria (12.84%, malaria-*Schistosoma mansoni* co-infection (12.10% and other intestinal helminth parasites such as hookworm, *T. trichiura*, *A. lumbricoides*, *S. stercoralis* and *Taenia* spp. 96 (11.85%). Males were more infected (32.72%) than females (23.09%). As age increased infection prevalence decreased and individuals within 5-9 & 10-14 age ranges were more affected than other age groups (Table 1).

PPF Status in *Schistosoma mansoni* Positive Individuals

Among 604 individuals who had ultrasonography for detection of schistosomal periportal fibrosis about 17.71% individuals had definite PPF and excreted *S.mansoni* eggs (40.54%) and were more affected than *S. mansoni* egg negative ones (10.31%) (P=0.000) (Table 2).

Among study subjects with periportal fibrosis, males were more affected by periportal fibrosis (68.23%) than females (31.77%) while children in the 5-10 years age group presented with the lowest overall definite periportal fibrosis (9.35%) (Table 3).

Individuals with moderate to severe PPF had significantly higher *S. mansoni* egg counts compared to individuals with mild or no PPF (Figure 2).

Table 1: Prevalence of parasitic diseases stratified by sex and age among study participants (n=810) in Finchaa Sugar Estate, Western Ethiopia, 2012-2014

Sex	Uninfected	Parasite							Overall Total n (%)
		Malaria n (%)	mal +Sm n (%)	Mal+ OIHP n (%)	Sm n (%)	Sm+ OIHP n (%)	OIHP n (%)	Total infected n (%)	
Male	164(20.25)	55 (6.79)	71(8.77)	17(2.10)	73(9.01)	5(0.62)	44(5.43)	265(32.72)	415(51.23)
Female	194(23.95)	49(6.05)	27(3.33)	9(1.11)	44(5.43)	6(0.74)	52(6.42)	187 (23.09)	395(48.77)
Total	**358(44.20)**	**104(12.84)**	**98(12.10)**	**26(3.21)**	**117(14.44)**	**11(1.36)**	**96(11.85)**	**452(55.81)**	**810(100)**
Age(Years)									
5-9	6(0.74)	3(0.37)	14(1.73)	5(0.62)	48(5.93)	8(0.99)	49(6.05)	127(15.68)	133(16.42)
10-14	31(3.83)	7(0.86)	19(2.35)	9(1.11)	35(4.32)	3(0.37)	37(4.57)	110(12.35)	141(17.41)
15-19	22(2.72)	18(2.22)	14(1.73)	8(0.99)	5(0.62)	0(0)	2(0.25)	47(5.80)	69(8.52)
20-24	56(6.91)	25(3.09)	23(2.84)	2(0.25)	12(1.48)	0(0)	4(0.49)	66(8.15)	122(15.06)
25-29	86(10.62)	15(1.85)	10(1.23)	2(0.25)	5(0.62)	0(0)	2(0.25)	34(4.20)	120(14.81)
≥30	157(19.38)	36(4.44)	18(2.22)	0(0)	12(1.48)	0(0)	2(0.25)	68(8.40)	225(27.78)

Mal=malaria, Sm=*S. mansoni*, OIHP-Other intestinal helminth parasites (Hookworm, *T. trichiura*, *A. lumbricoides*, *S. stercoralis* and *Taenia* spp).

Table 2: Categories of PPF by *S. mansoni* infection status among study participants in Finchaa Sugar Estate, Western Ethiopia, 2012-2014

Schistosoma mansoni status	Category of PPF based on image pattern*			Total n (%)	P
	No PPF n (%)	Indeterminate n (%)	Definite PPF n (%)		
Positive	46 (31.08)	42 (28.38)	60 (40.54)	148 (100)	0.000
Negative	335 (73.46)	74 (16.23)	47(10.31)	456 (100)	
Total	**381(63.08)**	**116 (19.21)**	**107(17.71)**	**604 (100)**	

*Richter *et al*. (2000).

Table 3: Prevalence and distribution of definite PPF by sex and age among study participants (n=107) in Finchaa Sugar Estate, western Ethiopia, 2012-2014

Sex	Definite PPF			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Male	48(44.86)	17(15.89)	8(7.48)	73 (68.23)
Female	22(20.56)	7(6.54)	5(4.67)	34 (31.77)
Total	**70(65.42)**	**24(22.43)**	**13(12.15)**	**107 (100.00)**
Age(years)				
5-10	8(7.48)	2(1.87)	0(0)	10 (9.35)
11-20	13(12.15)	7(6.54)	0(0)	20 (18.69)
21-30	27(25.23)	4(3.74)	5(4.67)	36 (33.64)
>30	22(20.56)	11(10.28)	8(7.48)	41 (38.32)
Total	**70(65.42)**	**24(22.43)**	**13(12.15)**	**107(100.00)**

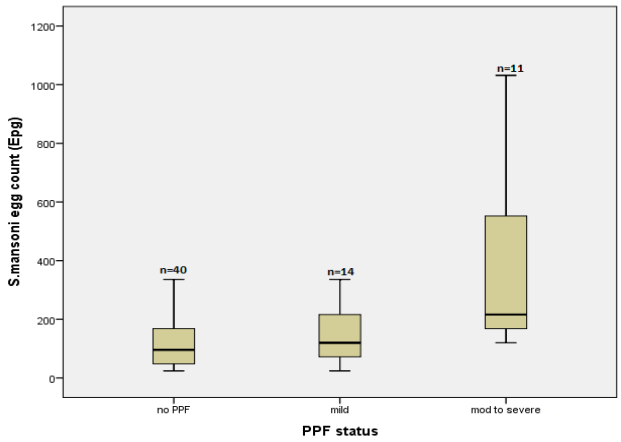

Figure 2: The expression of *S. mansoni* egg counts and PPF status, among study participants in Finchaa Sugar Estate, western Ethiopia, 2012-2014

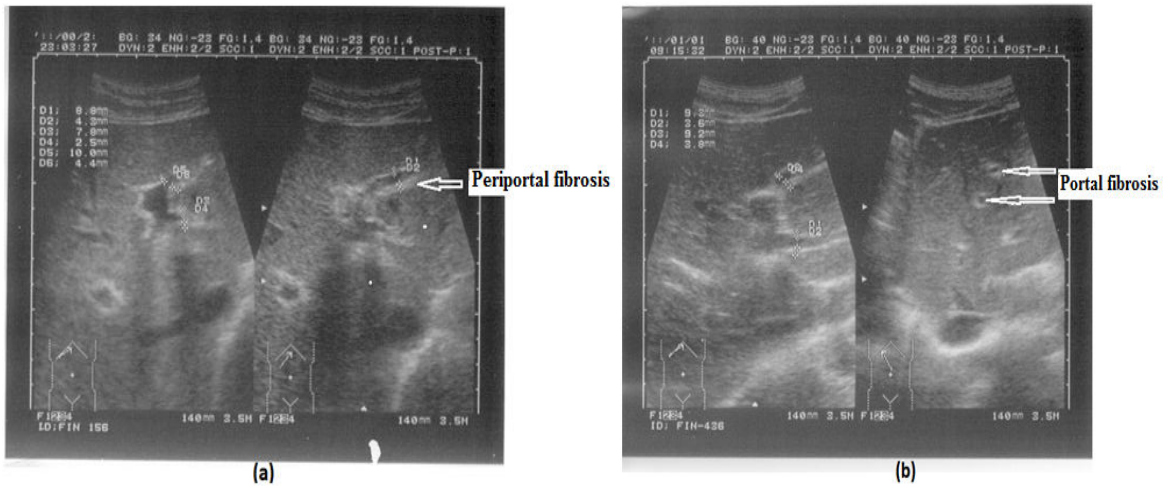

Figure 3: Ultrasonographic images in hepatic schistosomiasis: (a) Periportal fibrosis (Grade C Mild fibrosis) (b) Portal fibrosis (Grade D moderate fibrosis) among study

PPF status in Malaria-*Schistosoma mansoni* Co-infected Individuals

Of total 107 fibrotic individuals, more males were fibrotic (61.68 %) than females (38.32%). As age increased, the prevalence of liver fibrosis also increased in moderate cases (Table 4).

Univariate logistic regression analysis of PPF status (no PPF vs mild/severe PPF) as dependent variable and infections and co-infections as risk factors showed that malaria, *Schistosoma mansoni* and malaria-*Schistosoma mansoni* co-infections were identified as risk factors for PPF. However, malaria was not identified as risk factors for PPF (Table 5).

Table 4: Definite PPF category in liver fibrotic patients (n =107) stratified by sex and age among malaria-*Schistosoma mansoni* co-infection study participants in Finchaa Sugar Estate, Western Ethiopia, 2012-2014

	Definite PPF Category			
Study Group	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**
Sex				
Male	37(34.58)	27(25.24)	2(1.87)	66 (61.68)
Female	21(19.63)	18(16.82)	2(1.87)	41 (38.32)
Total	58(54.21)	45(42.06)	4(3.74)	107(100.00)
Age (years)				
5-9	4(3.74)	0(0)	0(0)	4 (3.74)
10-14	7(6.54)	0(0)	0(0)	7 (6.54)
15-19	13(12.15)	4(3.74)	0(0)	17(15.89)
20-24	16(14.95)	5(4.67)	0(0)	21(19.63)
25-29	10(9.35)	16(14.95)	0(0)	26(24.30)
≥30	8(7.48)	20(18.69)	4(3.74)	32(29.91)

Table 5: Malaria, *Schistosoma mansoni* and malaria-*Schistosoma mansoni* co-infections as risk factors for PPF (n=107) among malaria-*Schistosoma mansoni* co-infection study participants in Finchaa Sugar Estate, Western Ethiopia, 2012-2014

Risk factors			**95% C.I. for EXP(B)**		**P value**
	B*	**EXP(B)****	**Lower**	**Upper**	
Malaria	0.373	0.688	0.374	1.267	0.230
Schistosoma mansoni	1.985	0.137	0.077	0.246	0.000
Malaria + *Schistosoma mansoni*	1.360	0.257	0.106	0.620	0.002

*Coefficient of regression and **Odds Ratio

DISCUSSION

The prevalence of definite PPF among *S. mansoni* egg positive and egg negative individuals were 40.54 % and 10.31%, respectively with a significant difference indicating that *S. mansoni* egg positive individuals to be more fibrotic than *S. mansoni* egg negative individuals. The 10.31% PPF among egg-negative individuals could be attributed to false negative, among other factors.

As age increased, the prevalence of liver fibrosis increased. This is in line with Abebe *et al.* (2014), who reported that prevalence of PPF had a sharp rise in the 10 to 20 years age group and reached its peak in the age 20 to 30 years age group. The finding that children in the 5-10 years age group had the lowest risk of definite periportal fibrosis (9.35%) is consistent with the report of Booth *et al.* (2004a), who concluded that children presented the lowest risk of fibrosis. They suggested that this was probably because children are not exposed long enough for schistomal lesions to produce periportal fibrotic effect. The basis for the higher prevalence of PPF in males than in females, a finding that has also been

reported by other researchers (Henri *et al*., 2002; Booth *et al*., 2004a), may be explained by the relatively higher burden of infection in the males, a factor which is correlated with the intensity of exposure of the males to the infection as they work in the irrigated farms.

On the other hand, the relationship between *S. mansoni* egg count and PPF that showed individuals with moderate to severe PPF to have significantly higher *S. mansoni* egg counts compared to individuals with mild PPF, was contrary to what Abebe *et al*. (2014) reported from Gonder, northern Ethiopia. These contradictory results could be attributed to differences in PPF severity, schistosomal infection stage (acute or chronic), in which acute infection could lead to high egg counts. Furthermore, in the present study a positive association between intensities of *S. mansoni* infection and degrees of fibrosis was observed, which is in line with studies done elsewhere (Cheever and Andrade, 1967; Mohamed-Ali *et al*., 1999; van der Werf *et al*., 2003; Berhe *et al*., 2007), but contrary to Booth *et al*. (2004a) and Ribeiro de Jesus *et al*. (2004), indicating that the intensities of infection and degrees of fibrosis apparently fluctuate considerably between different endemic localities. The factors for such variations in the clinical outcomes could be the difference in the genetic variabilities of the parasite and the host (Aemero *et al*., 2015). In the present study, image pattern and portal vein wall thickness based ultrasound examination detected the two types of hepatic schistosomiasis: periportal fibrosis and portal fibrosis which is in line with studies conducted by Barsoum *et al*. (2013) and Baptista *et al*. (1988) who reported that periportal fibrosis can represent the first stage in the evolution of portal fibrosis, and often connotes an aggressive or progressive process.

CONCLUSIONS

The findings of this study showed that *S. mansoni* infection and co-infections are risk factors for PPF in the community and *S. mansoni* co-infection and co-morbidity reciprocally increase the degree of PPF. Thus, such understanding is a necessary factor in designing, developing and implementing intervention strategies to mitigate co-morbidity due to co-infection among the high risk groups.

Conflict of Interest

None declared.

Acknowledgements

The Office of Vice President for Research and Publication and Dean of School of Graduate Studies, Addis Ababa University, Ethiopia has provided financial support through the Thematic Research Projects entitled “Studies on genetic diversity of schistosomes and snail intermediate hosts in Ethiopia” and **“**Malaria and other Parasitic Diseases” for which we are grateful.

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