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REGRESSION OF LIVER FIBROSIS IN SCHISTOSOMA MANSONI INFECTED SUDANESE SUBJECTS AFTER PRAZIQUANTEL TREATMENT

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Abstract

Objectives: 1-To evaluate the effect of Praziquantel (PZQ) therapy on the regression of liver fibrosis in an endemic population.

2-To determine the factors controlling the regression of hepatic fibrosis (e.g. gender, age and grade of fibrosis).

Material and methods: An association study of a cohort of one hundred seventy seven Sudanese patients infected with *Schistosoma mansoni* (82 males 46%, 95 females 54%) was conducted to evaluate the factors controlling the regression of liver fibrosis 39 months after treatment with PZQ using ultrasound evaluation. SPSS (Statistical Package for Social Science) software was used for statistical analysis. Chi- Square was used to compare the two phenotypes (regression and progression) in the study subjects.

Results: PPF was regressed in 63 patients (36%) from higher grades of fibrosis to lower ones. While in 24 patients (13 %) the disease progressed to higher grades. In addition, the grade of PPF did not change in 90 patients (51%). The mean values of portal vein diameter (PVD), splenic vein diameter (SVD), and index liver size (ILS) in subjects in whom PPF regressed after treatment were significantly lower than in subjects in whom the disease was progressed ($P < .0001$, $P = .031$, and $P = .003$ respectively).The progression of hepatic fibrosis in

males (n = 15, 18 %) was greater than that of females (n = 9, 9 %). Patients who showed regression of PPF or progression of the disease tend to cluster in certain families.

Conclusion: Our study indicated that regression and stabilization of PPF after PZQ therapy is controlled by gender, age, grade of fibrosis, and possibly inherited factors.

Key words: Periportal fibrosis (PPF), Regression, Progression, Praziquantel (PZQ).

ملخص

مرض البلهارسيا المعوية يعتبر من الأمراض الطفيلية المعروفة في البلدان ذات المناخ الحار حيث أن المرض يشكل معضلة أساسية تهدد صحة الإنسان في تلك المناطق الموبوءة من العالم. وحسب تقديرات منظمة ا لصحة العالمية فان حوالي مئاتي مليون شخص مصابون بالمرض ، عشرون مليون منهم يعانون من مضاعفات المرض الحادة .

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أجريت هذه الدراسة في إحدى قرى السودان الموبوءة بمرض البلهارسيا المعوية (قرية أم ذكرى بوسط السودان) بهدف دراسة العوامل التي تتحكم في عملية تليف الكبد نتيجة للإصابة بالمرض ، وإمكانية تراجع التليف الي درجة أقل.

شملت الدراسة مائة سبعة وسبعين مريضاً حددت درجات تليف الكبد لديهم بواسطة الموجات الصوتية قبل وبعد تسعة وثلاثين شهراً من العلاج بواسطة عقار البرازكونتيل.

أشارت الدراسة إلى أن 36% من المرضى قد استجابوا للعلاج بدرجات متفاوتة وأن تليف الكبد لديهم قد تراجع الي درجة أقل بينما لم يتطور المرض فى 51% من المرضى . أيضا هنالك 13% من المرضىً تطور تليف الكبد لديهم إلى درجات أعلى.

أشارت الدراسة أيضا إن عوامل مثل عمر المريض والنوع (ذكر أو أنثى) ودرجة تليف الكبد وربما عوامل وراثية تتحكم في تراجع تليف الكبد الي الدرجات الأفضل.

Introduction

Human *Schistosomiasis* is a major health problem in many countries including Sudan. The disease is a chronic, debilitating and remains one of the most prevalent parasitic infections in tropical and subtropical environments [(1)]. Despite control efforts in a number of countries, still 200 millions of people are infected, 10 % develop severe disease with Symmers fibrosis [(2)]. Mortality due to *S. mansoni* infections is mainly the consequence of portal hypertension that is caused by hepatic periportal fibrosis (PPF) [(3)]. In PPF varying degrees of inflammation and collagen surround the portal vein and its tributaries are observed [(4)]. In some cases, there is virtual replacement of the portal system leading to portal hypertension, oesophageal varices, splenomegaly, massive hematemesis and death [(5)]. Chemotherapy with Praziquantel (PZQ) is the cornerstone of schistosomiasis control. Assessment of the impact of mass treatment with PZQ is usually by determining the prevalence of the infection and presence of PPF [(6)].

Previous ultrasonographic investigations in Sudan reported a reduction of egg excretion and a reversibility of PPF seven months [(6)], twenty-three months after PZQ treatment [(7)] ,and after both annual and biennial treatment [(8)].

Studies in animal models indicated that disease development is affected by interleukin 10 and 12 (*IL* 10, 12) which regulate the granulomatous response [(9,10)], and tissue -necrosis factor (*TNF-α*) [(11)]. It was found that, fibrosis following granulomatous inflamation was dependent on the fibrogenic action of cytokines such as *IL*-4 [(12)] , transforming growth factor *TGF-β1* and on the antifibrogenic effect of interferon-γ [(13,14)] .

In human *schistosomiasis* many reports mentioned the antifibrogenic effect of interferon-γ *(IFN-γ)* in hepatic fibrosis [(15,16,17 and 18)] .Recent studies had shown that human susceptibility to *S. mansoni* infection is controled by genetic loci: *SM1* located in chromosome 5q31-q33 which controls the infection levels in Brazilian population [(19)] and we have shown that susceptibility to PPF is controlled by *SM2* which located in chromosome 6q22-q23 and that is closely linked to *IFNGR1* (gene encoding the alpha chain of the IFN-γ receptor) in a Sudanese population [(20)]. In addition to other factors which include gender, age, duration and intensity of infection [(26)], we have shown in the same cohort of patients that severe PPF is associated with an increase in *TNF-α* production and the progression to severe PPF in Schistosomiasis was not associated with polymorphisms in the *TNF-α* gene [(21)]. It has also been reported that hepatomegaly associated with or without splenomegaly in patients with *S. mansoni* infection is influenced by *HLA* [(22, 23)]. *SM2* locus was found to be neither linked to *SM1* nor to the *HLA* locus [(19)]. Reports by Homeida group in their studies in Sudan have shown that the factors which control fibrosis regression involve age, gender and the grade of fibrosis. Young patients with lower PPF grades tend to respond more to antischistosomal chemotherapy [(4, 5 and 8)]

Based on the above findings, and since *SM2* locus was reported to control the progression of the disease [(20)] , it was suggested that the regression of PPF
(reversibility) also could be under genetic control. So, the aim of this study is to evaluate the factors controlling the regression of liver fibrosis in *Schistosoma mansoni* infected subjects after PZQ therapy.

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Materials & Methods

Study area and population:

This study was carried out between 1999 and 2005 in Um Zukra village, Gezira state, Managil province, central Sudan. The village is about 350 km South of Khartoum (The Capital) and 110 km West of Wad Medani town, in Managil extension agricultural scheme. Gezira and Managil irrigated scheme is about two million acres, cultivated by cotton and other crops, and populated by about 1.5 million individuals. The study area was selected according to the prevalence of *S. mansoni* infection. Randam stool samples were taken from different villages in the Gezira state, and examined for *S. mansoni* eggs. The highest prevalence (50 %) was found in UmZukra village. The population of Um Zukra is about 4000 individuals (according to a census performed in 1999) belonging to three tribes, mainly, the Kawahla (80%), in addition to Rawashda and Galeen (20%). The village is surrounded with cultivated area and the canal is only 450 m distance from the center of the village. There are two water pumps (wells) used for drinking water. The other water source for the domestic uses (washing and bathing) is the canal. Each house was given a number from 1 to 629.The numbers were written on metallic plates and fixed on all houses, and pedigrees for the study subjects were drown.

Stool examination and treatment:

Plastic containers for stool samples were distributed to the villagers according to the house and individual numbers. *S. mansoni* eggs count/gram stool has been done in November 1999 using the Kato´s method [24] on three stool samples collected on different days before treatment. All subjects were treated with PZQ tablets (40 mg / kg body weight), manufactured by: Medochemie LTD, Limassol, Cyprus, Lot No. E5K020.

Ultrasound evaluation:

Study subjects (n = 999) were evaluated by ultrasound (SSD 500 echo camera and 3.5- MHz convex probe; Aloka, Amsterdam, the Netherlands) before treatment in May 1999. Three hundred seventy seven subjects were evaluated again in August 2002 by the same ultrasonographer (Qurashi Mohamed-Ali). Only 177 subjects were included in the study because they had completed the planned ultrasound investigations. The degree of PPF was graded as F 0, F I, F II and F III according to the standardized Cairo classification [25] and as reported by many authors [26,27 and 4] .In brief; liver size, peripheral portal branches (PPBs), the degree of PPF, thickness of PPB wall, spleen size and splenic vein (SV) diameter were assessed. Livers and spleens were measured as previously described [28,8]) . Portal vein (PV) diameter was measured at its entrance to the porta hepatis at the lower end of the caudate lobe on subjects who had fasted ~ 8-10 h. Thickness of secondary (PPB) was observed for all subjects with FI-FIII grade of fibrosis. PPF was graded as grades 0 - III. Grade 0 (F0) corresponds to normal liver with no thickening of the PPB wall and PPB diameters (outer to outer) ~2-3 mm. Grade I (FI) corresponds to a pattern of small stretches of fibrosis around secondary portal branches and PPB diameters ~ 4 mm. Grade II (FII) still shows the patchy fibrosis observed in FI, but a continuous fibrosis affects most second-order branches, and PPBs appear as long segments of fibrosis. Grade III (FIII) shows a thickening of the walls of most PPBs.

Clinical evaluation:

A medical history, personal data (name, sex, age and number of pregnancy for married women), current symptoms, number of malaria attacks/year and physical examination for each subject were performed. Informed consent was obtained from each patient or parents in case of children.

Statistical analysis:

SPSS (Statistical Package for Social Science) software was used for statistical analysis. Chi- Square was used to compare the two phenotypes (regression and progression) in the study subjects.

Ethical approval for the study was obtained from the ethical committee of the University of Gezira, and from the State Ministry of Health, Wad Medani

Results

Fibrosis grades before and after treatment

The study was conducted in Um-Zukra, a Sudanese village highly endemic for *S.*

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mansoni. Fibrosis grades in 177 study subjects (82 males 46% and 95 females 54%) were reported before and 39 months after treatment (table 1)

Table 1: PPF grades before, and 39 months after treatment with PZQ (40 mg / kg body weight) in 177 study subjects.

Period	Fibrosis grades					
	F 0 (%)	F I(%)	F II (%)	F III (%)	Total	(%)
Before treatment	0 (0)	128 (72.3)	29 (16.4)	20 (11.3)	177	(100)
After treatment	49 (27.7)	74 (41.8)	31 (17.5)	23 (13)	177	(100)

The proportions of patients with FI and F0 before therapy was 72.3 % and 0 % respectively, and 39 months after treatment was 41.8 % and % 27.7) respectively. The difference was statistically significant *(P = 0.0001, P = 0. 000)* for F I and F 0 before and after treatment.

Prognosis of the disease

As shown in table 2, 77.7 % (n = 49) PPF in patients with F I and F II was regressed to F 0 39 months after treatment. In some patients (n =14), PPF regressed from F II to F I or from F III to F II were 8 (12.7 %) and 6 (9.6 %) respectively. In 24 patients PPF progressed, 15 (62.5 %) from F I to F II, 6 (25 %) from F II to F III and 3 (12.5 %) from F I to F III. The percentage of the patients in whom PPF was regressed from higher grades of fibrosis to lower ones (reversibility) was 36 % (n = 63) and for those in whom PPF was progressed from lower grades of fibrosis to higher ones was 13 % (n = 24), while in 51% (n = 90) of the study subjects, PPF was stable.

Table 2: State of PPF 39 months after treatment with PZQ (40 mg / kg body weight in 177 study subjects.

Phenotype	Fibrosis grades				Total	(%)
	FI-F0	FII-F0	FII-FI	FIII-FII		
Regression	(%) 46 (73)	(%) 3 (4.7)	(%) 8 (12.7)	(%) 6 (9.6)	63	(36)
	FI-FII	FII-FIII	FI-FIII			
Progression	(%) 15 (62,5)	(%) 6 (25)	(%) 3 (12,5)		24	(13)
	FI	FII	FIII			
Stable	(%) 66 (73.3)	(%) 10 (11.1)	(%) 14 (15.6)		90	(51)
Total					177	(100)

As shown in table (3), there was a significant difference in the mean values of the portal vein diameter, splenic vein diameter and index liver size *(P = 0.000, P = 0 .031* and *P =.003*) respectively, between patients in whom PPF was regressed from higher grades of fibrosis and in those whom PPF was progressed.

Table 3: Mean ± Standard Error of the mean, of ultrasound measurements of PPF status 39 months after

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treatment with PZQ (40 mg / kg body weight) in177 study subjects.

	Regression of PPF	Progression of PPF	Stability of PPF
PVD (mm)	n = 63 1.03 ± 2.7	n =24 1.32 ± 4.57	n=90 1.11± 3.05
SVD (mm)	n = 58 0.65 ± 2.2	n = 24 0.78 ± 4.5	n = 81 0.72 ± 2.9
S Vol.(cm^3)	n = 33 184.4 ± 22.4	n = 16 264.6 ± 47.5	n = 47 227.2 ± 35.4
IL.S	N= 36 72.6 ± 3.4	n = 15 94.9 ± 5.1	n = 45 75.9 ± 3.2

Abbreviations:
PVD = Portal vein diameter SVD = Splenic vein diameter
S Vol. = Spleen volume ILS = Index liver size

The mean values of PVD, SVD, and ILS in subjects with regressed PPF were statistically significant lower than those in subjects with progressed PPF (P = 0.0001, P = 0.031, and P = 0.003) respectively.

As shown in table 4, no significant difference in regression of PPF between males 30 (36.6%) and females 33 (34.7%), *P = 0.169*, although the figures are comparable. However, there is more progression of PPF in males 15 (18.3%) compare to females 9 (9.5%).The high number of females with stable PPF 53 (55.8%) was greater than the number of males 37 (45.1).This indicate that PZQ stabilizes PPF more in females.

Table 4: Response to PZQ treatment in males and females study subjects.

Sex	Regression of PPF (%)	Progression of PPF(%)	Stability of PPF(%)	Total(%)
Male	30 (36.6)	15 (18.3)	37 (45.1)	82 (46)
Female	33 (34.7)	9 (9.5)	53 (55.8)	95 (54)
Total	63 (36)	24 (13)	90 (51)	177 (100)

As shown in table 5, regression and stability of PPF phenotypes were more likely in patients of younger age (< 20 years) while progression phenotype was more frequent in older patients (> 20 years) *P = 0.065*

Table 5: Response to PZQ treatment after 39 months according to the age of the study Subjects.

Age group in years	Regression of PPF (%)	Stability of PPF (%)	Progression of PPF (%)	Total (%)
< 6	10	10	1	21 (12)
6 – 10	20	18	0	38 (21)
11 – 15	6	12	2	20 (11)
16 – 20	8	16	4	28 (16)
21 – 25	5	3	2	10 (6)
26 – 30	2	9	4	15 (8)
31 – 40	7	9	5	21 (12)
41 – 50	4	5	3	12 (7)
> 50	1	8	3	12 (7)
Total	63 (36)	90 (51)	24 (13)	177 (100)

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Patients who showed regression of periportal fibrosis or progression of the disease tend to cluster in certain families (Fig. 1 and 2).

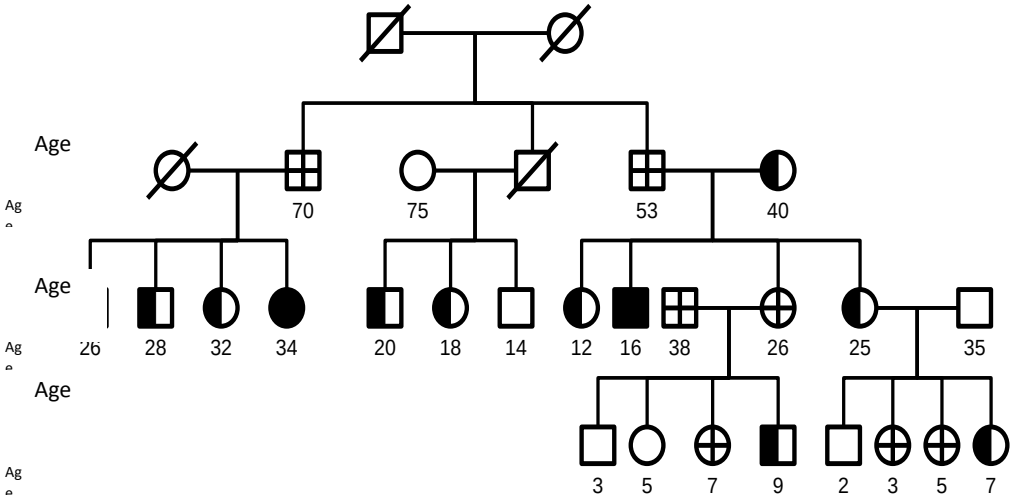

Figure 1. Shows clustering of regression phenotype (Half dark symbols) in certain families, stable phenotype (Crossed symbols) and not evaluated person (Open symbols).

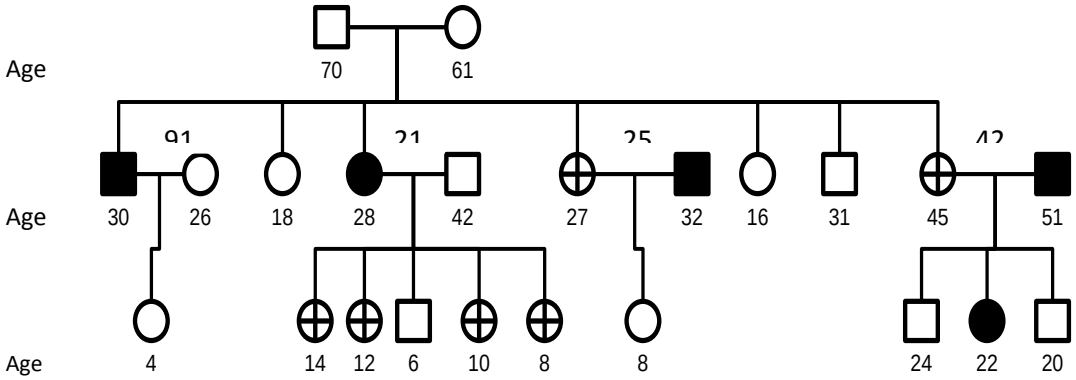

Figure 2.

Shows clustering of progression phenotype (Darked symbols) in certain families, stable phenotype (Crossed symbols) and not evaluated person (Open

Discussion

Disease prognosis

The main objectives of the present study were to evaluate the effect of PZQ therapy on the progression of PPF following treatment in a Sudanese population living in an endemic area for *S. mansoni* and to identify the major factors that may contribute to regression of periportal fibrosis. In this study, the percentage of patients with F I decreased from 72.3% (n = 128) before therapy to 41.8% (n = 74) 39 months after treatment. Although this finding was consistent with the previous studies done in Sudan, which reported regression of PPF after seven months, twenty three months and after both annual and biennial praziquantel therapy [6,7 and 8] however, in our study we were able to demonstrate a higher degree of total regression of PPF (36%, n = 63) of which 73% (n = 46) were regressed from F I to F 0, 4.7% (n = 3) from F II to F 0, 12.7% (n = 8) from F II to F I and 9.6% (n = 6) from F III to F II.

Why does PZQ causes regression of PPF?

PZQ treatment decreases the infection level by killing the parasites, decreases the number of eggs trapped

in the hepatic tissue, and this leads to decrease in granuloma formation which in turn decreases the fibrogenesis [31,4 and 32]. So collectively, PZQ prevent the formation of extra fibrous tissue. It is not known whether PZQ have an effect on existing fibrosis (Fibrolysis), but it is possible to activate the metaloprotienase enzyme which degrade the fibrosis tissue.

Age and grade of fibrosis

Age and grade of fibrosis both are associated with regression of PPF. The fact that low fibrosis grades are responsive to PZQ treatment could be due to the nature of the content of the fibrosis tissue. Early stages of PPF are more reversible after PZQ treatment[4], this could be due to collagen content that might have not undergone cross linking which usually stabilizes the tissue against fibrolysis [33] . PPF in younger patients is mostly at earlier stage which may explain why PPF is more reversible at younger age.

Gender and regression of PPF

Our findings indicated that the number of females in whom PPF regressed 33 (34.7%) is comparable to that in males 30 (36.6%). Nevertheless, PPF has progressed more in males 15 (18.3%) than in females 9 (9.5%). In addition,

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females benefited from PZQ treatment more than males. The number with stable PPF was 53 (55.8%) and 37 (45.1%) respectively. These findings indicate that females responded much better than males to PZQ treatment. Experimental animal studies support our observations [34.] .Female reproductive hormones have an antifibrogenic effects [35], while male reproductive hormones have a fibrogenic effect [36]. On the other hand, our findings showed that the disease in some patients (13%, n = 24) progressed from lower grades of fibrosis to higher ones following PZQ therapy. In 62.5% (n = 15) of them PPF progressed from F I to F II, in 25% (n = 6) PPF progressed from F II to F III and in 12.5% (n = 3) PPF progressed from F I to F III. Our explanation for this phenomenon was that either those patients were genetically susceptible to develop severe PPF and that fibrosis once started, progresses in spite of therapy or they did not respond adequately to treatment or the combination of both effects. The large number of patients in the present study (51%, n = 90) in whom PPF was stable (no change in fibrosis grades before and after treatment) does not mean that the pathology of the disease had stopped, but we think that those patients may need more time (> 39 months) in order either the disease reverse or may progress, or the praziquantel therapy should be repeated as reported previously [5,9]. However, PZQ was able to stabilize the disease. The resolution of PPF in our patients was accompanied by regression of splenomegaly (S Vol. = 184.4 ± 22.4) compared to those in whom PPF was progressed (S Vol. = 264.6 ± 47.5). This observation was inconsistent with Doehrig-Schwerdtfeger´s finding [7], who reported regression of hepatomegaly but not splenomegaly in patients who were investigated 23 months after PZQ therapy. However, our results were consistent with other investigators who reported regression of splenomegaly two years after either Praziquantel or Oxamniquine therapy [29, 30] . Our data show that, patients in whom PPF was regressed from higher grades of fibrosis to lower ones, were clustered in certain families. This observation may indicate possible involvement of inherited factors in the regression of PPF. Further investigations should be conducted to answer whether the regression of PPF is associated with genetic polymorphisms in certain genes such as *SM1* or *SM2*.

In conclusion, our study provides strong evidence for substantial regression and stabilization of PPF after PZQ therapy. Regression of liver fibrosis after PZQ therapy is affected by gender, age, grade of fibrosis, and possibly inherited factors.

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