Schistosoma mansoni infection and hepatocellular carcinoma in Egypt

Thesis

Submitted to Faculty of Medicine, Cairo university for Fulfillment of the M. S.C degree in Medical Parasitology

Presented By Yousra Nabil Abd El Hafez Mostafa

M.B. B.ch. Faculty of Medicine. Fayoum university

Supervised By

Prof.Dr. Abd El Hamid Abd El Tawab Sabri

Professor of Parasitology Faculty of Medicine. Fayoum university

Prof.Dr. Amany Ahmed Abd El Aal

Professor of Parasitology Faculty of Medicine. Cairo university

Dr. Naglaa Saad Mahmoud

Lecturer of Parasitology Faculty of Medicine. Cairo university

> Faculty of Medicine Cairo University

> > 2012





First and foremost, thanks to *Allah* the most kind and most merciful, to whom I relate any success in achieving any work in my life.

I wish to express my deepest gratitude, profound respect and appreciation to supervisors of this work

Prof. Dr. Abd El Hamid Abd El Tawab Sabri, Professor of Parasitology, Faculty of Medicine, Fayoum University, for his help, support and time he gave me to complete this work in its final form.

I would like to express my sincere gratitude to *Prof. Dr. Amany Ahmed Abd El Aal,* Professor of Parasitology, Faculty of Medicine, Cairo university for her kind meticulous expert supervision, unlimited help, for her precious opinions, continuous guidance and sincere support, which gave me the best guide during different stages of this work. She did her best to help me.

I feel deeply thankful to *Dr. Naglaa Saad Mahmoud*, Lecturer of parasitology,Cairo university, for her sincere assistance, remarkable effort and kind help.

I wish to express my gratitude and appreciation to *Dr. Enas Zakaria*, Assistant professor of Parasitology, faculty of medicine, Cairo university, for her kind help, time and effort she gave me.

Yosra Nabil

		1
	List of Contents	
		Page
List of abbreviation	S	Ш
List of figures		V
List of tables		VII
Abstract		VIII
Introduction & Aim of work		
Review of Literature.		
Chapter (1)		
Historical review and taxononmy		
Chapter (2)		
Epidemiology of Schistosoma mansoni		
Chapter (3)		
Clinical manifestation of Schistosoma mansoni		
Chapter (4)		
Immune response to schistosomes		
Chapter (5)		
Diagnosis		
Chapter (6)		
Hepatocellula	ar carcinoma and schistoso	omiasis 41
Patients & Methods		
Results:		64
Discussion:		80
Summary		92
Conclusion & Recommendations		
References		
Arabic Summary		



- **Ab** : Antibody.
- **CAgs:** Circulating antigens.
- **CD**: Cluster of differentiation.
- **CHR:** Cercarial hullen reaction.
- **CIET**:Counterimmunoelectrophoresis test.
- **CLD**:Chronic liver disease.
- **CMI**:Cell mediated immunity.
- **COP**: Circumoval precipitin test.
- **CT**: Computed tomography.
- **ECM**:Extra cellular matrix.
- **EITB**: Enzyme immunoelectrotransfer blot.
- **ELISA**: Enzyme-linked immunosorbent assay.
- **EM:** Electron microscope.
- **HBV**: Hepatitis B virus.
- **HCV**: Hepatitis C virus.
- **HCC**: Hepatocellular carcinoma.
- **HRP:** Horseradish peroxidase.
- **HPC**: Histopathologic changes.
- **HSCs**: Hepatic stellate cells.
- IARC: International Agency for Research on Cancer

- IFAT: Indirect immunoflurescent antibody test.
- IFN: Interferon.
- **IgE**: Immunoglobulin E.
- **IgG**: immunoglobulin G.
- **IgM**: Immunoglobulin M.
- **IHAT**: Indirect haemagglutination test.
- IL: Interleukin.
- **KDa**: Kilo Dalton.
- **KS:** Katayama Syndrome.
- **LCD**: Large cell dysplasia.
- MC: Mast cells.
- **MRI**: Magnetic Resonance Imaging.
- **MT**:masson trichrome.
- **nm**: Nanometer
- **PCR**: Polymerase Chain Reaction.
- **PGE1**: Prostaglandin E1.
- **Pzq**:praziquantel.
- **ROS, RNOS**: Reactive oxygen and nitrogen species.
- SCD: Small cell dysplasia.
- **SEA**: Soluble egg antigen
- S.haematobium: Schistosoma haematobium.
- *S.japonicum*: Schistosoma japonicum.
- S. mansoni : Schistosoma mansoni.

- **Th**: T helper.
- **TMB**: Tetramethylbenzidine.
- **TNF:** Tumor necrosis factor.
- **T reg**: Regulatory T-cells.
- **IDT:** Intradermal test.
- WHO: World Health Organisation.



1- Theodor Maximilian Bilharz.		
2- Global distribution of schistosomiasis mansoni.	7	
3- Acute liver granuloma around Schistosoma mansoni	10	
egg of an experimentally infected mouse.	10	
4- 6years old boy with gross reactive	16	
hepatosplenomegaly.	10	
5-representative images of hepatopathological changes	24	
over time.	24	
6-The major component of Schistosoma induced	77	
granulomas and the cytokines that drive this response.		
7-Kinetics of the Th1/Th2 response to Schistosoma	20	
infection.	29	
8- Regional variation in the estimated age standardized		
incidence rates of liver cancer.		
9- Microwells containing Schistosoma SEA Antigens -		
96 test wells in a test strip holder.		
10- ELISA results for HCC cases (60 cases) and control		
(20 cases).	08	
11- Important variables of the 60 HCC cases.	70	
12- Important demographic and laboratory results of the		
20 cases Schistosoma mansoni +ve HCC +ve.	13	

13-ELISA positive O.D values for gp (1) Schistosoma		
<i>mansoni</i> +ve, HCC +ve and negative O.D values for gp	74	
(2) Schistosoma mansoni -ve, HCC +ve.		
14- variables of group (1) Schistosoma +ve, HCC+ve in		
relation to group (2) Schistosoma -ve, HCC+ve.		
15- Shistosomiasis and viral hepatitis infection in the 60		
HCC cases.		
16-Schistosoma infection and Hepatitis C virus in 60	70	
HCC cases.	19	
17- Shistosomiasis and viral hepatitis infection in the 60	70	
HCC cases.	19	



- 1- Comprehensive questionnaire including Clinical and laboratory data of the cases. 63
- 2-Clinical and laboratory data of control group. 65
- 3-Different clinical and laboratory variables of the 60 hepatocellular carcinoma cases. 69
- 4-Different variables of the 60 hepatocellular carcinoma cases in relation to control. 71
- 5-Variables of group (1) Schistosoma mansoni positive hepatocellular carcinoma positive in relation to group (2) Schistosoma mansoni negative hepatocellular carcinoma positive.



Abstract

ABSTRACT

Schistosomiasis is the second most common parasitic infection of humans after malaria. In Egypt, schistosomiasis was traditionally one of the most important public health problems and infection with S. mansoni was the major cause of liver disease. In the past 10 years, hepatocellular carcinoma (HCC) was considered a major public health problem in Egypt, with a doubling in its incidence rate in this period. The rising incidence of HCC has been associated with increased prevalence of HCV infection, that was directly associated with intravenous tartar emetic used to control schistosomiasis from 1950s to 1980s. Currently, most Egyptian patients with chronic hepatitis, cirrhosis or HCC have co-infection of schistosomiasis and HCV. Literature had demonstrated that the association between *S.mansoni* and HCC is probably an indirect one, through potentiating the effect of hepatitis virus on the liver. However the role of isolated S. mansoni as a risk factor for the development of HCC is inadequately studied. In this study the role of isolated S. mansoni infection as a risk factor for development of HCC in Egypt was investigated. The current study included both parasitological and serological analysis that were conducted on 60 patients with HCC attending the outpatient clinic of medical oncology in health insurance hospitals in Fayoum governerate, performing stool examination and ELISA IgG antibody level for all 60 patients and 20 control group. Within HCC cases 26.7% (16/60), and 33.3% (20/60) suffered pure chronic schistosomiasis and pure Hepatitis C (HCV) infections respectively, with no statistically

significant differences (p=0.37), indicating comparable risk value of both infections in predisposing directly to HCC. Additionally; frequency of HCC patients with assumed potentiated HCV infection by chronic *Schistosoma mansoni* 6.7% (4/60) were statistically significant (p<0.05), when compared to HCC patients proceeded by either pure chronic schistosomiasis 26.7% (16/60) or pure HCV infection 33.3% (20/60).This indicated the presence of direct relationship between chronic schistosomiasis and HCC and other factors led to development of HCC patients and not only through potentiation of the effect of viral hepatitis on the liver.

Key words: *Schistosomiasis mansoni* - Hepatocellular carcinoma - Hepatitis C virus

N.B: The abstract is accepted and presented in the XI European Multicolloquium of Parasitology (EMOP XI), cluj-Napoca, Romania.



Introduction I Aim of the Work

INTRODUCTION

A

Schistosomiasis is a water-borne trematode infection that is endemic in 76 countries 46 of which are in Africa. About 207 million people are infected with 120 million people showing symptoms and 20 million severely ill (**Leonardo et al., 2012**). In Egypt, the incidence of this illness is still high inspite of the considerable effort to eradicate the disease. Sixty percent of the Egyptian population is at risk of infection. Children of school age are especially at risk because of their daily contact with infected water in rural areas (**Mostafa et al., 1999**).

In Egypt, schistosomiasis was traditionally one of the most important public health problems and infection with *S. mansoni* was the major cause of liver disease. From the 1950s until the 1980s, the Egyptian Ministry of Health (MOH) undertook large control campaigns using intravenous tartar emetic, the standard treatment for schistosomiasis, as community-wide therapy. This commendable effort to control a major health problem unfortunately established a very large reservoir of hepatitis C virus (HCV) in the country (**Strickland, 2006**).

Recent advances in the fields of molecular biology, epidemiology and infectious diseases have led to significant revelations to clarify the relationship between cancer and infective agents (**Khurana et al., 2005**).

1