Schistosomiasis and Hepatitis C

By

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Schistosomiasis

- Trematode parasitic infection
- Intermediate host: water snails
- Debilitating disease, severity depends on “worm load”

Theodor Bilharz (1825-1862) first described the trematode working at Kasr El Ainy hospital in Cairo in 1851.
Life cycle of schistosomiasis

- **Snail habitat:** irrigation canals, lakes, ponds
- Humans get infected through **skin contact** with water
- Humans excrete schistosomal eggs in urine or stool into water, keep-up life cycle of parasites
Hematemesis and melena are the most common clinical presentation of hepatic Schistosomisis.

Abdominal pain is usually caused by Hepatosplenomegaly.

Jaundice and manifestations of LCF are rare clinical presentation.
The association of hepatosplenic schistosomiasis and hepatitis C is very common especially in countries with high transmission of both infections e.g., Egypt, as well as in other endemic areas as Brazil.
- Epidemiology
- Effect of Combined infection
  - Immunopathogenesis
  - Severity
  - SVR
Epidemiology

Effect of Combined infection
- Immunopathogenesis
- Severity
- SVR
Global distribution of Schistosomiasis

Senegal
An epidemic of schistosomiasis along the Senegal river basin caused by water-resource development schemes continues unabated.

Egypt
Praziquantel chemotherapy coupled to a vigourous media campaign has resulted in a significant decrease in the morbidity and prevalence of schistosomiasis infection.

Iran, Morocco, and Saudi Arabia
Schistosomiasis control has been successful in those areas with elimination of the infection contemplated.

China
Schistosoma continues to be a major public health problem in the lake and marshy regions despite successful control in other endemic areas.

Lao People’s Democratic Republic
Schistosoma mekongi control has been successful around Khong Island with prevalence reduced from 42% to <2%.

Djibouti and Somalia
Displacement of people by war and instability has introduced intestinal schistosomiasis to these countries.

North-east Brazil
Urban schistosomiasis now present in and around many major cities.

Ghana
Intestinal schistosomiasis has increased due to the construction of the Akosombo Dam and other much smaller dams.

sub-Saharan Africa
More than 85% of the estimated 200 million people globally with schistosomiasis and the majority of patients with severe disease live on this continent.

Indonesia
Schistosomiasis has been controlled in the Lindu region of Sulawesi such that the prevalence of infection is lower than 2%.
Parenteral Antiscistosomal Therapy (PAT)
Treatment of Schistosomiasis in the Past

Antimony salt “tartar emetic” as an antibilharzial agent given IV was introduced by McDonagh and was popularized by Christopherson (1918) in Egypt.

Mass PAT campaigns to control schistosomiasis had great potential to transmit blood-borne pathogens, specifically HCV, due to insufficiently sterilised injection in a mass setting.
The risk factor for HCV transmission that specifically sets Egypt apart from other countries is a personal history of parenteral antischistosomal therapy (PAT).

This intensive transmission established a large reservoir of chronic HCV infection, responsible for the high prevalence of HCV infection and current high rates of transmission.
The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt


Lancet 2000; 355: 887–891

Further evidence for association of hepatitis C infection with parenteral schistosomiasis treatment in Egypt

Malla R Rao*1, Abdollah B Naficy1, Medhat A Darwish2, Nebal M Darwish2, Enrique Schisterman1, John D Clemens1 and Robert Edelman3

BMC Infectious Diseases 2002, 2

Liver Disease in Egypt: Hepatitis C Superseded Schistosomiasis as a Result of Iatrogenic and Biological Factors

G. Thomas Strickland

Hepatology 2006; 43: 915-922
Geographic HCV Geographic HCV Prevalence 1996*

- **Alexandria**: 5.9% (95% CI: 4.2-7.7)
- **Lower Egypt**: 28.4% (95% CI: 27.1-29.2)
- **Middle Egypt**: 26.5% (95% CI: 23.7-29.4)
- **Upper Egypt**: 19.4% (95% CI: 17.2-21.6)
- **Cairo**: 8.2% (95% CI: 6.7-9.8)

* age-adjusted prevalence, population between 10 and 50
Ever had injection Schistosomiasis

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<tr>
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<th>Men</th>
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<td>31.3</td>
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<tr>
<td>Schistosomiasis</td>
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<tr>
<th></th>
<th>No</th>
<th>Don't Know / Missing</th>
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<td>11.2</td>
<td>23.8</td>
</tr>
<tr>
<td></td>
<td>15.5</td>
<td>10.9</td>
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HCV Egypt 2008 and Anti-Schistosomiasis injection
hepatitis C infection in Egypt

- Approximately 90% of Egyptian isolates belong to a single subtype, 4a. (Ray et al., 2000, Kamal et al., 2000).

- Furthermore, HCV is less prevalent in countries neighbouring Egypt having similar socio medical conditions and similar strains (WHO 1997).
This problem is not prominent in other countries endemic for schistosomiasis probably because control efforts for treatment of Schistosomiasis by (PAT) were less population intensive and less geographically extensive.
The treatment of choice for all species is **praziquantel (oral)**

It leads to increased permeability to calcium ions → muscular contractions and paralysis of adult worms → dislodgement from their sites and subsequent expulsion by peristalsis

40 mg/kg /BW in one or two doses (tablet=600 mg)
Schistosomiasis prevalence decreased in Egypt due to:

1. Health education.
2. Availability of Praziquantel in the rural health units.
4. Mass treatment in the villages with prevalence > 20%.
5. Snail control.
Parenteral antischistosomal treatment (PAT) programs are believed to have infected a large proportion of the exposed population with HCV from 1950s until the early 1980s (Nafeh et al., 2000 & Rao et al., 2002).
Relative Importance of Risk Factors for Hepatitis C by Endemicity Level

**High Endemicity**
- Nosocomial
- Transfusion
- Other

**Low Endemicity**
- Injection Drug Use
- Sexual
- Other
Transmission of Nosocomial Infections

- Healthcare worker to patient
- Patient to healthcare worker
- Patient to patient
■ Epidemiology

■ Effect of Combined infection
  – Immunopathogenesis
  – Severity
  – SVR
Background of immunological defense

- *S. mansoni* causes liver pathology through immune-mediated mechanism, rather than through direct hepatic injury.
- Ova are trapped in the liver, evoking a highly skewed Th2 immune response with granuloma formation coupled with a defect in Th1-cell function.

*S. mansoni* egg granuloma in the liver. The tissue reaction around an ova trapped in the portal triad consists of macrophages, lymphocytes & fibroblasts.
Immunopathogenesis of Combined Infection

- Dual infection of schistosomiasis and HCV display significant influence on host immune reactions including cytokine shift pattern alteration, cytotoxic T lymphocytes response and other impaired immunologic functions with diminished capacity to clear the virus (El-Kady et al., 2004).
Immunopathogenesis of Combined infection

Viral clearance

THo

Th1

IL-2
IFN-γ

IL-4
IL-5
IL-10

Th2

IL-4
IL-5
IL-10

+ + +

+ + +

+ + +

Viral clearance

THo

Th1

IL-2
IFN-γ

IL-4
IL-5
IL-10

Th2

IL-4
IL-5
IL-10

+ + +

+ + +

+ + +

Immunopathogenesis of Combined infection
Schistosomiasis appears to induce Th2 cytokine profile, with ↑ IL-4, IL-10. It downregulate the stimulatory effect of HCV on Th1 cytokines and this may lead to chronicity of HCV infection in coinfectected patients (El-Kady et al., 2004 & 2005).
Different Cytokine Patterns in Patients Coinfected with Hepatitis C Virus and Schistosoma mansoni

Ibrahim M. El-kady, Samir A. El-Masry, Gamal Badra and Khalil A. Halafawy
It has been shown that soluble egg antigen possesses a potent in vitro proliferative activity on peripheral blood mononuclear cells and directly stimulates HCV replication in vitro.
- Epidemiology
- Effect of Combined infection
  - Immunopathogenesis
  - Severity
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Pathologically schisto-HCV co-infection has possibly a synergistic effect especially on hepatic fibrosis.

By serial liver biopsies, progression of hepatic fibrosis was shown to be faster in patients with co-infection than in those with HCV (0.6 point/year vs 0.2 point/year).

This may refer to altered immune response or fibrogenesis signals.
Clinically:

Patients with HCV & *S. mansoni* coinfection show markedly accelerated hepatic fibrosis.

This may be reflected on the coinfected patient by an earlier onset of:
- Portal hypertension
- Bleeding oesophageal varices
- Hypersplenism
Decompensated CLD

- ↑ grade C Child-Pugh score,
- ↑ episodes of upper GI bleeding,
- ↑ renal impairment
- ↑ mortality rate

Gad et al., 2001)
**Disease Progression in Chronic Hepatitis C: Modifiable and Nonmodifiable Factors**

**Table 1. Factors Associated with Disease Progression in Chronic Hepatitis C**

<table>
<thead>
<tr>
<th>Nonmodifiable factors</th>
<th>Potentially modifiable factors</th>
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<tbody>
<tr>
<td>Age at acquisition of infection</td>
<td>ALT level</td>
</tr>
<tr>
<td>Duration of infection</td>
<td>Activity on liver biopsy</td>
</tr>
<tr>
<td>Male sex</td>
<td>Alcohol consumption</td>
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<tr>
<td>Race</td>
<td>Coinfection with HBV or HIV</td>
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<tr>
<td>Host genetic factors</td>
<td>Coinfection with schistosomiasis</td>
</tr>
<tr>
<td>Viral genotype</td>
<td>Metabolic factors (steatosis, insulin resistance)</td>
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<tr>
<td></td>
<td>Cigarette smoking</td>
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<td></td>
<td>Daily cannabis use</td>
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<td>Iron overload</td>
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Schistosoma mansoni coinfection could have a protective effect against mixed cryoglobulinaemia in hepatitis C patients

Omaima M. Abbas¹, Nabil A. Omar², Hassan E. Zaghla² and Mohammad F. Faramawi³

Association between S. mansoni co-infection and protection against cryoglobulinaemia in HCV patients

Liver International 2009
What about the relation of combined infection on HCC prevalence?

- HCC is never observed in *S. mansoni* infection alone and may be present only in coinfection with HBV or HCV (Ahmed et al., (1998) and Kamal et al., 2000).
- Epidemiology

- Effect of Combined infection
  - Immunopathogenesis
  - Severity
  - SVR
Is schistosomal infection has an influence on anti-viral therapy?

The presence of associated schistosomiasis has determined the response of Egyptians with chronic hepatitis C to therapy with interferon (Abdel Basset et al., 1994).
EL-Shazly et al., (1994); reported low rate of response in combined infection than in HCV alone.

Schistosomiasis effect on anti-viral therapy of HCV patients

- Active Schistosomiasis
  (Detection of ova or antigens)
  Low SVR

- Past Schistosomiasis
  (Detection of antibodies)
  no effect on SVR
disease. Dual infections of schistosomiasis and viral infections display significant influences on host immune reactions including cytokine shift pattern alteration. It also has an impact on response to antiviral therapy. Thus screening for active schistosomiasis and treating the infection prior to initiating IFN/ribavirin therapy is mandatory.
There was no significant difference in response in bilharzial & non-bilharzial patients in both groups, where SR was achieved in 27 patients co-infected with bilharziasis (60.7%) and in 7 cases of HCV alone (58.3%)

**Conclusion:** concomitant HCV-genotype 4 & bilharzial infections do not seem to affect the improved responses achieved with pegylated interferon
In a cohort of 1988 patients infected with HCV genotype 4 treated with IFN-based therapy; there was no significant difference in ETR or SVR for those patients with past history of schistosomiasis (Antibodies positive), and patients who had no past history of schistosomiasis.

(Esmat et al., 2012, in press)
To sum up:

- Chronic hepatitis C may be associated with schistosomiasis in endemic areas which in turn influences manifestations, prognosis and outcome of HCV infection.

- Dual infections of schistosomiasis & HCV exhibit a unique clinical, virological, and histological pattern manifested by virus persistence with high HCV RNA titers, higher necroinflammatory and fibrosis scores in liver biopsies, and poorer response to interferon therapy.
Thank you
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