Schistosomiasis: Filling in the Gaps

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INSTITUTE OF TROPICAL MEDICINE ANTWERP

Outline

Gaps in diagnosis and treatment of acute schistosomiasis
E. Bottieau

Gaps in diagnosis and treatment of chronic schistosomiasis
F. Gobbi

VO, Belgian, 30 years; consultation ITMA on May 14, 2012

- No medical history
- Back from Guinée since May, 1st (9 months for MSF)
- Recent problems
  - End of March: fever; Paracheck (HRP2 RDT) positive for P. falc malaria; start Coartem (3 days); better
  - Fever again 2 weeks later: RDT neg; suspicion of typhoid fever: ciprofloxacin 5 days; better
  - Fever again 2-3 weeks later: Coartem empirically; not really better: persistence of fever and onset of dry cough (at night)
VO, Belgian, 30 years; consultation ITMA on May 14, 2012

- Better since a few days (after being back in Belgium)
- Comes for a checkup
- Additional information
  - No contact with sick people
  - No sexual risk
  - Did swim in a river near Guéckédou (in March); took praziquantel immediately after swimming
  - Did swim again in a waterfall pool near Kindia (Mid-April)
  - Took mebendazole preventively after return

Blood results

- Leucocytes: 57,500 [nl < 11,000/µL]
- Eosinophils: 44,620 (77.6%)
- C-RP: 13.5 [nl < 10 mg/L]
- LDH: 1,119 [nl < IU/L]
- IgE: 1,767 [nl < IU/L]
- HRP2-based RDT: positive
- Pan LDH-based RDT: positive
- Blood microscopy: negative

Urine examination

- Normal urinalysis
- Culture neg
- Parasite microscopy neg

Feces examination

- Charcot-Leyden crystals +++
- Cysts of Entamoeba dispar/histolytica (PCR: E. dispar)
- Giardia antigen test positive
- Eggs of Schistosoma mansoni (30/gr)
Diagnoses
- Recent *P. falciparum* malaria (adequately treated)
- Acute schistosomiasis/Katayama (*S. mansoni*)
- Giardiasis (asymptomatic)

Treatment
- Praziquantel (PZQ) 60 mg/kg/day for 2 days (3-3)
- Medrol 32 mg 16-16-8-8-8-8
- (new malaria testing in case of fever recurrence)

Serology
- *P. falciparum*: 1/320
- Schistosoma ELISA: positive
- Schistosoma IHA: 1/840 (nl = 1/160)
- *S. stercoralis* (and other relevant serologies) negative

Molecular workup
- PCR for Schistosoma sp. in stool and blood (121 bp)
**Schistosomiasis: recent cases/clusters in travelers (ITMA)**

- 2012; n=3
- 2011; n=9
- 2010; n=48
- 2008; n=1
- 2008; n=1
- 2008; n=1
- 2009; n=13
- 2008; n=1

**Schistosomiasis: life cycle and timing of early events**

- Exposure
- Serocconversion
- Onset eosinophilia
- Eggs faeces/urine
- 2-8 weeks
- Abdominal pain
- Cough
- Onset fever
- 2 weeks to 3 months

**Katayama fever (ITMA 2000-4): clinical features (n=23)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Myalgia</td>
<td>17</td>
<td>74</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td>Cough</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>Abdominal symptoms</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>High fever (&gt;39°C)</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>21</td>
<td>91</td>
</tr>
<tr>
<td>Recurrence of symptoms</td>
<td>5</td>
<td>22</td>
</tr>
</tbody>
</table>

**Katayama fever (ITMA 2000-4): diagnosis at presentation**

*Low sensitivity of conventional tests even when combined*

- Egg detection: 22%
- Serology (both IHA and ELISA): 26%
- Serology IHA alone: 26%
- Serology ELISA alone: 0%
- At least one positive test: 65%

**Katayama fever (cluster 2009 Rwanda) diagnosis (n=13)**

*Increased diagnostic yield with molecular assay*

- Egg detection: 69%
- Serology (both IHA and ELISA): 77%
- At least one positive test: 85%
- Serum *Schistosoma* DNA (PCR): 100%

**Schistosoma real-time PCR at ITM (research only)**

- 'genus' PCR (28S rRNA): Crops et al., 2012
  - Stool (1g) and urine (300µl); not on serum
  - Detection of all species (*Sm*, *Sh*, *Si*, *Sj*, *Smek*, no differentiation)

- *S. mansoni* complex: highly frequent tandem repeat

- *Dra1* PCR: Crops et al., 2013
  - Serum (2ml => 1ml => 400µl) (whole blood) (all other clinical samples)
  - *S. haematobium* complex: highly frequent tandem repeat
### Rwanda cluster 2009:
**Real-Time PCR (Sm1-7) in serum in acute schistosomiasis with S.mansoni**

<table>
<thead>
<tr>
<th></th>
<th>eosinophil</th>
<th>ELISA</th>
<th>HAI</th>
<th>IEPG</th>
<th>PCR</th>
<th>CI PCR</th>
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<tbody>
<tr>
<td>1</td>
<td>5400</td>
<td>p</td>
<td>320</td>
<td>30</td>
<td>p</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>2900</td>
<td>n</td>
<td>320</td>
<td>130</td>
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<td>3</td>
<td>2840</td>
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<td>n</td>
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<td>4</td>
<td>14150</td>
<td>p</td>
<td>640</td>
<td>40</td>
<td>p</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>2800</td>
<td>p</td>
<td>n</td>
<td>20</td>
<td>p</td>
<td>31</td>
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<td>4370</td>
<td>p</td>
<td>320</td>
<td>90</td>
<td>p</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>11120</td>
<td>p</td>
<td>160</td>
<td>10</td>
<td>p</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>1960</td>
<td>p</td>
<td>320</td>
<td>n</td>
<td>p</td>
<td>32</td>
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<td>10</td>
<td>1260</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>36</td>
</tr>
<tr>
<td>11</td>
<td>1210</td>
<td>p</td>
<td>n</td>
<td>10</td>
<td>p</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>3100</td>
<td>p</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>27</td>
</tr>
<tr>
<td>13</td>
<td>1700</td>
<td>p</td>
<td>320</td>
<td>10</td>
<td>p</td>
<td>35</td>
</tr>
</tbody>
</table>

PCR promising tool for early diagnosis

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### French male, 63 years; consultation Bordeaux June 5, 2012
- **Trip (one month)** to Ivory Coast
- Single exposure in a lake on May, 1st
- Fever on May, 25th; eosinophilia on May, 29th
- On June 5, Bordeaux: fever with no other symptom
  - Eosinophilia: 1,410/µL (19%)
  - Serology Schistosoma sp: IHA and ELISA neg
  - Microscopy feces/urine: neg
- Trip to Cameroon (June, 8) against medical advice
- Development of transverse myelitis; repatriated with paraplegia one month later; incomplete recovery despite steroids and praziquantel

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### Case report: early neuroschistosomiasis in a traveler
- **T2-weighted sequence:** intramedullary contrast enhancement of the conus medullaris (1a and 1b)
- **T1-weighted sequence:** heterogeneously enhancing lesion of the conus medullaris with irregular enhancement extended on the spinal roots of the cauda equina following intravenous gadolinium injection (2a and 2b)

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### IW, Belgian, 30 years; consultation ITMA on Jan 26, 2017
- No medical history
- Back from South Africa (North of Kwazulu-Natal) since Jan 5
- Fever and cough since a few days
- Two children have the same symptoms (since 3-10 days)
- Referred by GP because of eosinophilia (760/µL)

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### IW, Belgian, 30 years; consultation ITMA on Jan 26, 2017
- Stay in Eco-Lodge in South Africa (from 26th December to 5th of January 2017
Cluster of 34 Belgian travelers, exposed to Witrivier

Exposure to Witrivier (uMkhunyana River)
2-5 Jan, 2017

<table>
<thead>
<tr>
<th>Cluster of 34 Belgian travelers, exposed to Witrivier</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
</tr>
<tr>
<td>Swimmers’ itch</td>
</tr>
<tr>
<td>Any acute symptom</td>
</tr>
<tr>
<td>Among persons with symptoms (n=32)</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Muscle ache</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

Onset of symptoms: 19 – 41 days, (median 25 days)

Time line acute schistosomiasis: 34 travellers

Exposition

Symptoms 19-51d (94%)

Fever

Headache

Muscle ache

Cough

Abdominal pain

Diarrhea

33 persons first seen between D27 and D37 (median D29)

One person first seen at D50

Institute of Tropical Medicine Antwerp
Cluster of 34 Belgian travelers, additional testing (LUMC)

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-treatment (%)</th>
<th>Posttreatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests</td>
<td>N/n (%)</td>
<td>W4-S</td>
</tr>
<tr>
<td>Eosinophils &gt; 750 µL</td>
<td>22/34 (65)</td>
<td>3/34 (9)</td>
</tr>
<tr>
<td>Schisto ova urine/feces</td>
<td>0/33 (0)</td>
<td>0/34 (0)</td>
</tr>
<tr>
<td>Schisto IFT ELSA</td>
<td>12/34 (35)</td>
<td>10/34 (32)</td>
</tr>
<tr>
<td>Schisto IFT IHA</td>
<td>3/32 (9)</td>
<td>0/34* (0)</td>
</tr>
<tr>
<td>Schisto LUMC IFA</td>
<td>15/33 (46)</td>
<td>25/34 (74)</td>
</tr>
<tr>
<td>PCR Dru1</td>
<td>24/33 (73)</td>
<td>24/34 (71)</td>
</tr>
<tr>
<td>UCP-CAA serum LUMC</td>
<td>30/33 (91)</td>
<td>1/34 (3)</td>
</tr>
</tbody>
</table>

Cluster of 34 Belgian travelers, exposed to Witrivier

- Very poor performance of conventional methods
- Microscopy: 0% sensitive
- Serology: 33% sensitive
- Molecular assay (Dra1): 100% sensitive
- Genotyping: hybrid S. haematobium / S. mattheei
- Circulating anionic antigen (CAA): promising for early diagnosis

Schistosomiasis in the Phongola Basin

- S. haematobium
  - Schistosoma haematobium type: schistosoma haematobium or distinct genotype, (one of the most important schistosome species worldwide)
  - IUCN: near threatened

Acute schistosomiasis, principles of treatment

- Control of hypersensitivity symptoms: anti-inflammatory drugs
- Preference to steroids
- But no solid data on optimal timing, dosage, duration, in particular in children
- Antiparasitic treatment: praziquantel (PZQ), but
  - Little activity on larval stages
  - Risk of early oviposition (early neuroschistosomiasis)
  - Risk of clinical exacerbation, and drug interaction with steroids
- No evidence of usefulness for acute schistosomiasis in non-immune travelers

Cluster of 34 Belgian travelers, exposed to Witrivier.

You give steroids at diagnosis for one week to those who are symptomatic
You prefer to treat the symptoms with non-steroidal anti-inflammatory drugs (since many patients have > 18 years)
You give steroids for one week + praziquantel 40 mg/kg SD at diagnosis
You give steroids for one week + praziquantel 40 mg/kg/day for 2 days

Acute schistosomiasis, principles of treatment
Schistosomiasis treatment: praziquantel (PZQ) 40 mg/kg

- Single dose 40 mg/kg (Zwang J. Paras & Vectors 2017)
- Different PZQ dosages (Zwang J. PLoS NTD 2014)

Cure rate: 75%
Egg reduction rate: 85-95%

Schistosomiasis treatment: adverse event PZQ

- Assessed in > 12,000 subjects
- Up to 56% (95% CI 47-68)
- Light to moderate

Praziquantel forever? Massive use in “prevention”

- Effective
- Safe
- Cheap

Praziquantel: little effect on larvae

- Almost no effect up to 5-6 weeks after infection

Acute schistosomiasis, early ovideposition (6 weeks?)

- Early Neuroschistosomiasis Complicating Katayama Syndrome
- Boy with left-sided hemiparesis and slurred speech 8 weeks after exposure

Acute schistosomiasis, clinical exacerbation after PZQ

- In up to 50% of the patients
- (Botteau E et al. J Infect 2006)
- Sometimes impressive
Acute schistosomiasis, praziquantel treatment

- C max: 1.5h after ingestion; half-life: 0.8 to 1.5 hours!
- Therapeutic effect 4 to 10 h after single dose
- Metabolization in inactive derivatives: CYP450
- Urinary excretion (70% in ≤ 24h), no nephrotoxicity

- Parast load reduction of single dose PZQ 40mg/kg: > 80%
- PZQ concentration when steroids are given concomitantly
- If given in fractioned doses: a 4 to 6 h interval is recommended

SA cluster of acute schistosomiasis, treatment at week 4-5

- Methylprednisolone 0.5mg/kg
- Praziquantel 20mg/kg at 0h and at 2h
- Followed at hour 4 by methylprednisolone 0.5mg/kg/day for 3 days (to repeat if necessary)

- Only if symptoms
- ➢ for symptomatic patients
- ➢ cycle of 3 days
- ➢ to repeat if recurrence of symptoms

- 32/34 were symptomatic
- 21/34 were sick enough to be given steroids
- 15/21 (73%) needed 1 cycle
- 6/21 (27%) needed 2(4) or 3(2) cycles

Acute schistosomiasis, proposed “ITMA” treatment

- If diagnosis made BEFORE week 6 (post-exposure/infection)
  - Only in case of symptoms
  - Methylprednisolone 0.5 mg/kg/day for 3 days (to repeat if necessary)

- If diagnosis made AFTER week 6 (post-exposure/infection)
  - Praziquantel 20 mg/kg at hour 0 and at hour 2
  - Followed at hour 4 by methylprednisolone 0.5 mg/kg/day for 3 days (to repeat if necessary)
  - Praziquantel 40 mg/kg single dose at week 12

Acute schistosomiasis, SA cluster in ITMA

- Lessons learned
  - Early symptomatic schistosomiasis (< 6 weeks): short course of steroids is sufficient most of the time
  - From week 6 onwards single dose praziquantel combined with steroids prevent acute symptoms

- Question to resolve
  - Single dose praziquantel: sufficient?
  - Timing for repeated dose?
  - No risk of neuroschistosomiasis before week 6?
  - Treatment dependent on parasite load?
Schistosomiasis treatment: artemisinins?

- More effective on larval stages/juvenile worms
- Higher efficacy ART-PZQ compared to PZQ alone
- More effective than placebo in chemoprophylaxis

Perez del Villar. PLoS ONE 2012

Schistosomiasis treatment: other drugs clinically tested

Table 2 Summary of four recent clinical trials with drugs repositioned for use against chronic infections with S. mansoni and S. haematobium

<table>
<thead>
<tr>
<th>Compound</th>
<th>1. mansoni</th>
<th>2. haematobium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefloquine</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Pyronaridine</td>
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<td>91</td>
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<tr>
<td>Pyramethazine</td>
<td>Not done</td>
<td>Not done</td>
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<tr>
<td>Thiabendazole</td>
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<td>Not done</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>97</td>
<td>91</td>
</tr>
<tr>
<td>Inclometizole</td>
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<td>73</td>
</tr>
<tr>
<td>Parvomycetemycin</td>
<td>40</td>
<td>96</td>
</tr>
<tr>
<td>Alkyl bis (ether) arsonic acid</td>
<td>50</td>
<td>0.01</td>
</tr>
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</table>

Bergquist R. Infect Dis Poverty 2016

Schistosomiasis treatment: alternative drugs summary

Thank you!