Female genital schistosomiasis

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University of KwaZulu-Natal, South Africa
Oslo University Hospital, Norway
1) Urogenital schistosomiasis

2) Rural research - from the ivory tower to advanced and practical research (10.30 Ondini)
This presentation

1. The studies to date and their weaknesses
2. Clinical appearance and HIV
3. Symptoms and age aspects
4. Diagnosis - well, well
5. Treatment, a gamble
6. Hope in the pipelines – your input
London 30\textsuperscript{th} of January 2012:

Nine Pharmaceutical Companies will

- Share their libraries
- Make their secrets available for researchers
- Donate billions of tablets for neglected tropical diseases
  - 400 million tablets for soil-transmitted worms
  - 250 million tablets for Bilharzia, etc.
The history of genital schistosomiasis

Madden (Egypt) 1899

Gelfand (Zimbabwe) Youssef (Egypt)

Berry & Friedberg (S.Africa)

Renaud (Niger)

Malawi*

odd case reports infertility, pain at intercourse, bleeding problems, ugly lesions, removal of the uterus, association with cervical cancer

*Poggensee, Feldmeier, Richter, Gundersen, Kjetland
South African RCT* n = 1800
Madagascar n = 120
Tanzania, n = 457
Zimbabwe, n = 527
Tanzania, n = 434
Madagascar, n = 116 and 254
Malawi, n = 52
Niger, n = 61
1989
2011

Observational studies, endemic ‘controls’

* Cluster randomised
Idyllic transmission site
2. Clinical appearance and HIV

3.

4.

5.

6.
Human types

- *Schistosoma haemtobium* - urinary
- *S. mansoni* - intestinal
- *S. japonicum* – intestinal
- *S. intercalatum*
- *S. mathei* etc

Genital schistosomiasis = Genital Bilharzia
Human types

- *Schistosoma haemtobium* - UROGENITAL
- *S. mansoni* - intestinal
- *S. japonicum* – intestinal
- *S. intercalatum*
- *S. matthei* etc

Genital schistosomiasis = Genital Bilharzia

WHO 2009
Grainy sandy patches

the os

2 cm

the cervix
Results from study in Zimbabwe

Is genital schistosomiasis associated with HIV?

n=479
Schistosomiasis ova in genital mucosa

<table>
<thead>
<tr>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>41% HIV (29/70)</td>
<td>26% HIV (96/375)</td>
</tr>
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</table>

RR 2.1  95%CI 1.2-3.5  p= 0.008

Kjetland et al 2006, n=479
## Association with HIV

### Bivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95%CI)</th>
<th>p</th>
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<tr>
<td><strong>S. haematobium</strong></td>
<td></td>
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<td>in Pap smear</td>
<td>2.3 (1.04-5.2)</td>
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<td>HSV-2</td>
<td>2.7 (1.7- 4.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>Woman infertile</td>
<td>1.9 (0.8- 4.5)</td>
<td>0.12</td>
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<tr>
<td>Widow</td>
<td>1.4 (1.2- 1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (1 yr increase)</td>
<td>0.96 (0.94-0.98)</td>
<td>0.002</td>
</tr>
<tr>
<td>HPV</td>
<td>3.9 (2.0- 7.8)</td>
<td>&lt;0.001</td>
</tr>
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<td>Past syphilis</td>
<td>2.8 (1.3- 6.2)</td>
<td>0.009</td>
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<tr>
<td>Paid labour</td>
<td>7.9 (0.8- 77)</td>
<td>0.074</td>
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Kjetland et al 2006, n=479
## Association with HIV

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<th>Bivariate analysis</th>
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Kjetland et al 2006, n=479
Supporting evidence

HIV does not increase ova excretion
(reports from urine and faeces)

N'Zoukoudi-N'Doundou ‘95, Mwanakasele ‘03, Kallestrup ‘05
Genital schisto

Worse?
More?

HIV

No, lesions are not larger in HIV positive lesions are not more numerous in HIV positive lesions do not have more contact bleeding

Kjetland et al 2006, n=479
Supporting evidence

17-fold increased rectal susceptibility to SHIV in monkeys with acute *S. mansoni*
Increased density of the HIV-receptors CCR5 and CXCR4 on blood-CD4 cells and monocytes in patients with schisto

Supporting evidence

Secor ‘03
15-24 year-olds, AIDS epid update ‘08
In some areas:

genital schistosomiasis is
the most common gynecological lesion

Supporting evidence

Poggensee 01, Leutscher ‘08, Kjetland ‘05
Supporting evidence

cells are immunologically active

Wright ’82, El-Shoura ’93, Helling- Giese ‘96
Supporting evidence – calcified eggs

cells are immunologically active

CD4 receptors

Jourdan ‘11
Supporting evidence

Global HIV/AIDS distribution

Adult prevalence (%)
- 11.0% - 20.0%
- 5.3% - 10.0%
- 1.3% - 5.0%
- 0.5% - 1.0%
- 0.1% - 0.5%
- 0.01% - 0.1%
- not available
Supporting evidence

*S. haematobium* and HIV/AIDS distribution overlap
Supporting evidence

*S. haematobium* and HIV/AIDS distribution overlap
All important STD-HIV intervention studies

Mwanza
Rakai
Kisumu
Manicaland
etc
HIV prevention research
State of the science

- Male circumcision
- Herpes supression, STD treatment
- Microbicides
- Cervical barriers
- HIV vaccines
- Pre-exposure prophylaxis with antiretrovirals
- Prevention of FGS
1. The studies to date and their weaknesses
2. Appearance and HIV
3. Symptoms and age aspects
4. Diagnosis
5.Treatment, a gamble
6. Hope in the pipelines

Genital schistosomiasis = Genital Bilharzia
<table>
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<tr>
<th>Disease</th>
<th>Prevalence</th>
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<tr>
<td>Herpes SV-2 seropositive</td>
<td>307/ 476 (65)</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>74/ 222 (33)</td>
</tr>
<tr>
<td>HIV</td>
<td>153/ 523 (29)</td>
</tr>
<tr>
<td>Trichomonas seropositive</td>
<td>118/ 477 (25)</td>
</tr>
<tr>
<td>Past syphilis</td>
<td>30/ 481 (6)</td>
</tr>
<tr>
<td>Candida</td>
<td>32/ 408 (8)</td>
</tr>
<tr>
<td>Trichomoniasis in smear</td>
<td>30/ 474 (6)</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>14/ 409 (3)</td>
</tr>
<tr>
<td>Current syphilis</td>
<td>13/ 479 (3)</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>6/ 429 (1.4)</td>
</tr>
<tr>
<td>Neisseria gonorrhoea</td>
<td>4/ 429 (0.9)</td>
</tr>
<tr>
<td>Haemophilus ducreyi</td>
<td>0/ 30 (0)</td>
</tr>
<tr>
<td>Genital schistosomiasis</td>
<td>259/ 527 (49)</td>
</tr>
</tbody>
</table>
Symptoms

• Adults think they have an STD
• Malodorous discharge
• Secondary infertility
• Spot bleeding

When does this start?

Kjetland 2008, Leutscher 2001
Girls aged 10-12, n= 1057

• 32% have Bilharzia in urine
• 63% have high risk water contact
• 44% of the ones with Bilharzia have a genital symptoms (vs 18%)
  – Smelly discharge (17%)  Genital itch (24%)
  – Bloody discharge (11%)  Ulcers (10%)
  – Burning sensation (17%)  Tumours (5%)

Submitted: Hegertun et al 2012
Egg excretion

Age (years)
Egg excretion

Nothing in urine
41% had schisto in the genitals

Fulford 98
Genital *S. haematobium* lesions
Prevalence relations

Genital Bilharzia

Urinary Bilharzia in adult women

Malawi
Niger
Zim
Tanzania
Madagascar

Swai 2006, Kjetland 2005
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Genital schistosomiasis = Genital Bilharzia

4. Diagnosis
Diagnostic possibilities

• Serology – 75%, could be old infection
• PCR genital specimen – does not detect old lesions (with Dead ova and no DNA)
  – More sensitive in the young
• Antigens
  – Microscopy urine
  – Rectal snip (careful, tolerant uneducated patients)
  – Genital biopsy (careful, tolerant uneducated patients)
• Clinical manifestations
<table>
<thead>
<tr>
<th>Genital schisto</th>
<th>neg</th>
<th>pos</th>
</tr>
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<tbody>
<tr>
<td>Urinary</td>
<td>177</td>
<td>123</td>
</tr>
<tr>
<td>schisto</td>
<td>80</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>257</td>
<td>234</td>
</tr>
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3 urines, Zimbabwe, Kjetland 2005
Copenhagen / Durban consensus

In patient from an *S. haematobium* endemic area: one of three clinical findings, by visual inspection may serve as an adequate diagnosis for genital schistosomiasis:

Aceto-negative:

(i) grainy sandy patch or
(ii) homogenous yellow sandy patch or
(iii) rubbery tubercles

Kjetland 2014
1. The studies to date and their weaknesses
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Genital schistosomiasis = Genital Bilharzia
Treatment of schistosomiasis

Easy –

One dose one day praziquantel
Decreases ova in urine / stool
What about gynaecological lesions
Treatment with praziquantel in 527 women

No significant effect of pzq on the genital mucosal bleeding and sandy patches

Confounders:
- Herpes II
- Syphilis
- HIV
- Gonorrhoea
- Chlamydia
- Chancroid
- Trichomonas
- Papilloma Virus
- Candidiasis
- Atypical cells
- Bacterial vaginosis

Other confounders:
- Age
- Timing of treatment
- Doses
- Baseline lesion
- Size
- Type
- Localisation
- Intensity of infection

Kjetland et al ‘06
Treatment with praziquantel in 527 women

No significant effect of praziquantel on the genital mucosal bleeding and sandy patches

Investigated at
3 months 73 % attendance
12 month 64 % attendance

83% were seen at least once after baseline

Kjetland et al ‘06
Retrospective

• Women – some had they been treated before
• 3 different types of medication
• Was there any effect
Retrospective

Kjetland et al ‘08
Retrospective
Age at anti-schistosomal treatment as a predictor for:

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<td>Rx at 12</td>
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<td>Rx at &lt;12</td>
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<td>Current age</td>
<td>1.01 (1.0-1.0)</td>
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<td>Regular H2O</td>
<td>111/122 (91) 1.49 (0.8-3.0)</td>
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Kjetland et al ‘08
Age at anti-schistosomal treatment as a predictor for:

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<td>Current age</td>
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<td>0.584</td>
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Kjetland et al ‘08
Conclusions about treatment

Lower prevalence of genital sandy patches and contact bleeding with younger age at treatment

No influence of:
- current water contact
- interval between treatment and investigation
- type of treatment

Likely better to treat the young

Kjetland et al ‘08
Treatment – likely 4 factors influencing effect

1. Age

2. Localisation

3. Intensity of infection

4. Degree of scarring - chronicity

Doehring 86, Smith 86, Devidas 89, Vester 97, Hatz 98, Kabatereine 99, Subramanian 99 Wagatsuma 99, Abdel-Hadi 00, Engels 02, Bergquist 02, Colley 04, Savioli 04, Silva 05
Why hasn’t more been done on genital schistosomiasis?
Further research

• ideal timing of treatment / prevention of HIV
• impact on fertility / cancer / STDs
• non-invasive and syndromic diagnostic methods
• are men at risk of HIV from dually infected women
• how to treat adults
• *S. mansoni* – does it cause FGS
Thanks to valuable previous & current co-authors & donors


In chronological order from 1994
• UNDP/ WB/ WHO/TDR
• Oslo University Hospital
• Norwegian Research Council
• Danish Bilharziosis Laboratory
• NORAD
• Bill and Melinda Gates Foundation
• EU

And thanks for listening
Reprints: e.f.kjetland@medisin.uio.no
Website and (soon) pocket atlas: www.brightresearch.org