The Biology and Control of Human Onchocerciasis

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1. Filarial nematode
2. Transmitted by blood-sucking flies
3. Humans are the only natural host
4. Adult female worms are sedentary and usually occur in nodules
5. Microfilariae cause skin and ocular disease and infect the vector

*Redrawn and modified from original figure by Lane & Crosskey (1993)

Distribution of human onchocerciasis

- Originally described in Sub-Saharan Africa (Ghana, 1893)
- Transported to the Arabian peninsula (Yemen) and the Americas
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Adult worms (AFIP photographs)

Evidence of infection – nodules often can be seen and palpated
Worms are embedded in connective tissue

After collagenase digestion

Microfilarial stage

• Embryonic – lacks complex internal development
• Moves through the skin and secretes elastase and other enzymes
• As numbers increase, the MF stage invades the eye and cause a variety of ocular pathologies

Degree of infection can be determined by skin examination

Corneal-scleral punch for biopsy

Epidemiological surveys determine prevalence and intensity of infection (microfilariae per milligram of skin, CMFL)
Class: Insecta, Order: Diptera, Family: Simuliidae

Black fly life cycle
Egg, Larva, Pupa, Adult

- Larvae (B) are aquatic "filter feeders" that occur in riffle areas of rivers and streams.
- Female flies are aggressive blood-feeders & many species can fly long distances.

Transmission of the parasite

Only female flies take blood.
Microfilariae are ingested in the blood meal.
Transmission indices
(epidemiology, control)

1. Monthly biting rate = \( \frac{\text{# of flies caught} \times \text{# of days in month}}{\text{# of catching days}} \)
2. Monthly transmission potential = \( MBR \times \frac{\text{total # of } L_3 \text{ in head}}{\text{# of flies dissected}} \)
3. Annual transmission potential = \( \sum \text{of MTP} \)

Pool screen
(Katholi et al., 1995; J. Inf. Dis. 172: 1414 – 1417)
1. Uses \( O. volvulus \) – specific primers for polymerase chain reaction
2. Calculates prevalence of infection; Recent version calculates ATP

Important vectors* (Simulium spp.)
of Onchocerca volvulus - Africa & Yemen

<table>
<thead>
<tr>
<th>Location</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Africa</td>
<td>( S. damnosum ) cytospecies complex ** (( S. sirbanum, S. damnosum s. s ))</td>
</tr>
<tr>
<td>Central Africa</td>
<td>( S. damnosum ) species complex, ( S. albivirgulatum, S. kilibanum )</td>
</tr>
<tr>
<td>East Africa</td>
<td>( S. damnosum, s. l., S. kilibanum; S. neavei ) group</td>
</tr>
<tr>
<td>Yemen</td>
<td>( S. rasyani )</td>
</tr>
</tbody>
</table>

* Simulium damnosum sensu lato Theobald shown to be the intermediate host in Sierra Leone in 1926
** Responsible for 95% of transmission

Important vectors (Simulium spp.)
of Onchocerca volvulus - the Americas

<table>
<thead>
<tr>
<th>Location</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico &amp; Guatemala</td>
<td>( S. ochraceum*, S. metallicum )</td>
</tr>
<tr>
<td>Colombia</td>
<td>( S. exiguum )</td>
</tr>
<tr>
<td>Ecuador</td>
<td>( S. exiguum, S. quadrivittatum* )</td>
</tr>
<tr>
<td>Venezuela/Brazil</td>
<td>( S. metallicum, S. exiguum, S. guianense, S. oyapockense*, S. incrustatum* )</td>
</tr>
</tbody>
</table>

* Four species possess a cibarial armature (“armed vector”)
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Ocular pathology due to onchocerciasis

- Punctate ("snow flake") keratitis
- Sclerosing keratitis
- Infiltration of the retina
- Invasion of the optic nerve

Blindness (at risk populations)

- Fishing & related activities by the water
- Villages within flight distance of the vector

Blindness (exposure)

- Most blindness occurs as a result of chronic exposure
- Where transmission is intense, blindness can occur in the mid- to late-teens

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Blindness (socio-economic effects)
- Blindness rates in hyperendemic areas often reached 8-12%
- Blinded persons became non-productive and wards of the village

Blindness

Robles disease in the Americas
- 70% of persons at risk occur in Mexico and Guatemala
- Coffee production is an important occupational risk factor

Control of river blindness
1. Nodulectomy in Mexico and Guatemala
2. Large scale vector control (East and West Africa)
3. Control of the parasite using chemotherapy

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Nodulectomy by lay surgeons (Mexico, Guatemala)

A. Nodules are palpated
B. Head is shaved
C. Nodule is injected with a local anesthetic and removed

Vector control

- Rationale:
  - Use synthetic insecticides to control the vector and thereby limit the number of infective bites per person per year
  - “Break” the life cycle of the parasite by reducing number of L3s below a certain threshold
- Proof of concept:
  - First demonstrated in Kenya

Kenya

- Efforts began in 1946 and control was completed by 1955 using DDT as the primary larvicide*
- *Simulium neavei* was eliminated from \( \approx 40,000 \text{ km}^2 \) (about 15,000 square miles)*
- 11 years after interruption of transmission, live *O. volvulus* adults were present in nodules and microfilariae were present in the skin**
- Microfilariae were no longer found in the skin after 18 years**

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Vector control

- OCP – Launched in West Africa in 1975 where “blinding form” of O. volvulus was prevalent
- Life span of female O. volvulus ≈ 12-15 years
- Vector control in savanna habitat (20 year program in 11 countries using Temephos)

Outcomes of the OCP

- Difficulties:
  - Problems with insecticide-resistance to organophosphate compounds
  - Unanticipated, annual west-to-east migration of parous, O. volvulus - infective flies

Outcomes of the OCP*

- Successes:
  - Skin disease was significantly reduced throughout the region
  - > 200,000 cases of blindness were prevented
  - Size and distribution of the O. volvulus population in the region was substantially decreased
  - 12 million infants born after inception of the program faced no risk of contracting onchocerciasis
  - ≥ 25 million hectares of fertile riverine land re-opened

*The OCP was successfully closed in 2002
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Paradigm shift – emergence of ivermectin as a control measure

• A new type of drug (macrocyclic lactone - ivermectin) reported in 1980 as being efficacious against the microfilariae of Onchocerca cervicalis with none of the gross or clinical reactions commonly associated with diethylcarbamazine treatment
• Preliminary clinical trial of 32 patients in Senegal found the drug to be efficacious and safe
• A series of in-depth studies in Africa spanning 4-6 years determined dosage efficacy, tolerance and effects on parasite transmission

Ivermectin - a drug that is microfilaricidal and can be used safely in humans*

1. Microfilariae are eliminated from the skin in 2-3 days

Results of other in-depth studies

• Clinical:
  – Doses of 150 μg/kg are effective and eliminate microfilariae from the skin for 4-6 months following treatment*
  – Early eye disease can be reversed by ivermectin**

**Taylor et al., 1986, Arch. Ophthalmol. 104, 863-870

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Results of other in-depth studies (2)

- Operational:
  - A single treatment prevents vector infection for 4-6 months*
  - Mass treatment impacts transmission on a large scale, thereby preventing new infections**

* Cupp et al., 1986, Science 231, 740-742
** Taylor et al., 1990, Science 250, 116-118

Control of human onchocerciasis is now based on use of ivermectin (Mectizan®)

- 1987 - Merck & Co. decides to provide ivermectin (Mectizan®) free of charge as long as needed for treatment of human onchocerciasis
- Unprecedented in the history of tropical medicine
- Raised the possibility that the 2nd leading cause of infectious blindness could be globally controlled
- Mectizan® donation program (MDP) established to assist in the evaluation of programmatic, financial, and logistical capabilities for each country requesting the drug

Development of regional programs the Americas

- Onchocerciasis elimination program for the Americas (OEPA) founded in 1992
- 13 foci distributed among six countries (Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela) with more than 536,000 people at risk
- Mandate: mount a regional control program with elimination of O. volvulus as the eventual goal
- Strategy: 2×yr treatment of eligible population with 85% coverage
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Development of regional programs the Americas clinical outcomes (2009):

- Treatment coverages exceeding 85% of the eligible population achieved in 8/13 foci by 2001 and in all foci by 2006
- No new cases of onchocercal blindness occur in the region
- Ocular disease attributable to *O. volvulus* has been eliminated from nine of the 13 foci

Development of regional programs the Americas transmission (2010)

Development of regional programs Africa

- 1996 - African programme for onchocerciasis control (APOC) is formed (19 non-OCP countries)
- Up to 600,000 people blind or have severe visual impairment; 80% of the population suffers from onchocercal skin disease and itching
- Primary goal: establish within the next 12 years effective, sustainable, community-based ivermectin treatment programs ("CDTT")
- Disease control (1x/year treatment) versus elimination (2x/year)
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Development of regional programs Africa (2)

• APOC is slated to run until 2015
• Treatment of over 90 million people annually, protecting an at risk population of 115 million
• Prevent over 40,000 cases of blindness each year
• APOC also provides technical support to former OCP countries
• Difficulty: *Loa loa* encephalopathy associated with ivermectin treatment

Summary – progress and needs

• *Mectizan* is an effective monotherapy to control disease caused by *O. volvulus*
• 2x/year treatment has proven to be effective not only for disease control but interruption of transmission as well (the Americas, Uganda, Yemen, Sudan)
• Senegal and Mali have also succeeded in interrupting transmission using 1x & 2x per year treatments
• Most important threat:
• Most important need:

Acknowledgements

• Source of figures:
  – Photographs attributed to “CDC” were made from histological material prepared for Dr. Richard Collins (slides 6,15,16,18) or were made in the field by CDC staff working in Guatemala (slide 14)
  – Photographs attributed to “AFIP” (slides 7,15) were made by Dr. Dan Connor, Armed Forces Institute of Pathology
  The figure attributed to “WHO” (slide 10) was taken from *Onchocerciasis: Symptomatology, Pathology, Diagnosis; Edited by A. A. Buck. 1974, WHO, Geneva*
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