Filariae

Edward Mitre, MD
Department of Microbiology and Immunology
Uniformed Services University of the Health Sciences
February 2011
Talk Outline

• Background on filarial infections
• Lymphatic Filariasis
• Onchocerciasis
• Loa loa
What are filariae?
Filarii

threadlike  
(from Latin *filum* = thread )

tissue-invasive

roundworms

transmitted by insect vectors
What was the genius of Patrick Manson?

Scottish physician
Tropical medicine pioneer
1844-1921
What was the genius of Patrick Manson?

Hypothesized and then proved via experiment with Hin-Lo that filariae are transmitted via mosquitoes.

The first-ever demonstration that mosquitoes can harbor infectious disease.
General life cycle of filariae
Humoral parameters of helminth infections over time

- Polyclonal IgE
- Specific IgE
- Polyclonal IgG4

Antibody vs. Time

Allergic Reactivity vs. Time

Helminth Burden
What is totally bizarre about the following case?

29yo M
--1996 exhibited right hand swelling x 1 day, but nothing since.
--In 2001 a friend of his on the same expedition mentioned that he had recently been diagnosed with Loa loa.
--So, patient decided to get himself checked out for Loa loa, even though he felt perfectly well.

Daytime blood filtration →
Helminth-specific T-cell responses over time

Infection with filaria prevents autoimmune diabetes in NOD mice
## Filarial Infections of Humans

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>LOCATION</th>
<th># INFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>Tropics worldwide</td>
<td>129 million</td>
</tr>
<tr>
<td><em>Brugia spp.</em></td>
<td>Asia</td>
<td>10 million</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>Africa, Americas</td>
<td>18 million</td>
</tr>
<tr>
<td><em>Loa loa</em></td>
<td>Africa</td>
<td>13 million</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Microfilariae</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>lymphatics</td>
<td>blood (usually night)</td>
</tr>
<tr>
<td>Loa loa</td>
<td>SQ tissues (moving)</td>
<td>blood (day)</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>SQ tissues (nodules)</td>
<td>skin</td>
</tr>
</tbody>
</table>
# Treatment of Filariais

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic filariasis</td>
<td>DEC</td>
<td>-----</td>
</tr>
<tr>
<td>Loa Loa</td>
<td>DEC</td>
<td>DEC and Ivermectin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>if high mf level</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>ivermectin</td>
<td>DEC</td>
</tr>
</tbody>
</table>

**ADVERSE EFFECTS**
- Loa with high microfilaremia $\rightarrow$ encephalopathy and death
- Onchocerciasis $\rightarrow$ severe skin inflammation and blindness
Talk Outline

• Background on filarial infections
  • Lymphatic Filariasis
  • Onchocerciasis
  • Loa loa
Lymphatic filariasis

- *W. bancrofti, Brugia malayi* and *Brugia timori*
- Vector: mosquitoes (Anopheles, Aedes, Culex, Mansonia)
- Host: human
- Microfilariae: blood-borne
- Adult worms: lymphatics
- Reservoir: Wb – none  Bm – cats, macaques (rare)
Lymphatic filariasis: epidemiology

Figure 2. Global distribution of lymphatic filariasis and status of mass drug administration (MDA), 2009
Filariaiasis
(Wuchereria bancrofti)

Mosquito Stages

1. Mosquito takes a blood meal (L3 larvae enter skin)
2. L3 larvae
3. Migrate to head and mosquito's proboscis
4. L1 larvae
5. Microfilariae shed sheaths, penetrate mosquito's midgut, and migrate to thoracic muscles
6. Mosquito takes a blood meal (insecta microfilariae)
7. Adults in lymphatics
8. Adults produce sheathed microfilariae that migrate into lymph and blood channels

Human Stages

1. Infective Stage
2. Diagnostic Stage
LF: clinical manifestations

- Asymptomatic microfilareemia
- Filarial fevers
- Lymphangitis
- Lymphatic obstruction
  - Lymphedema, elephantiasis, hydrocele, chyluria
- Tropical pulmonary eosinophilia
LF: clinical manifestations

lymphangitis
LF: clinical manifestations

hydrocele

lymphedema
LF: clinical manifestations

elephantiasis
LF: clinical manifestations

19yo Haitian man
May 2009

Courtesy Dr. Todd Gleeson, USS Comfort
LF: clinical manifestations

Courtesy Dr. Todd Gleeson, USS Comfort
LF: clinical manifestations

Courtesy Dr. Todd Gleeson, USS Comfort
**LF: a very morbid disease**

**Table 3. Infectious and parasitic diseases burden, worldwide and by region, 2001**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease burden worldwide, DALYs in thousands (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Disease burden by region, %&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Africa</td>
<td>Southeast Asia</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>88,429 (6.0)</td>
<td>65.0</td>
</tr>
<tr>
<td>Diarrheal disease</td>
<td>65,451 (4.3)</td>
<td>32.9</td>
</tr>
<tr>
<td>Malaria</td>
<td>42,280 (2.9)</td>
<td>65.2</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>36,040 (2.5)</td>
<td>24.8</td>
</tr>
<tr>
<td>Measles</td>
<td>26,495 (1.8)</td>
<td>57.1</td>
</tr>
<tr>
<td>Sexually transmitted disease&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12,401 (0.8)</td>
<td>41.4</td>
</tr>
<tr>
<td><strong>Lymphatic filariasis</strong></td>
<td>5,644 (0.4)</td>
<td>34.2</td>
</tr>
<tr>
<td>Trachoma</td>
<td>3,997 (0.3)</td>
<td>38.2</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>2,357 (0.2)</td>
<td>17.0</td>
</tr>
<tr>
<td>Hookworm disease&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1,825 (0.1)</td>
<td>23.3</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>1,760 (0.1)</td>
<td>80.8</td>
</tr>
<tr>
<td>Trichuriasis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1,649 (0.1)</td>
<td>7.5</td>
</tr>
<tr>
<td>African trypanosomiasis</td>
<td>1,598 (0.1)</td>
<td>97.4</td>
</tr>
<tr>
<td>Ascariasis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1,181 (0.1)</td>
<td>10.2</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>987 (0.1)</td>
<td>95.0</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>767 (0.1)</td>
<td>0.0</td>
</tr>
<tr>
<td>Dengue</td>
<td>653 (0.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>649 (0.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>Leprosy</td>
<td>177 (0.0)</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>All infectious and parasitic diseases</strong></td>
<td>359,377 (24.5)</td>
<td>52.6</td>
</tr>
</tbody>
</table>
Tropical pulmonary eosinophilia

- Paroxysmal nocturnal asthma
- Pulmonary infiltrates
- Peripheral blood eosinophilia (>3,000/mm$^3$)
- Marked elevation of serum IgE
- Very high filarial antibody titers
- Rapid response to anti-filarial chemotherapy
Lymphatic filariasis: diagnosis
Lymphatic filariasis: diagnosis

- **Definitive diagnosis**
  - Identification of microfilariae in nighttime blood (sheathed)
  - Detection of circulating antigen in blood (only Wb)
  - Identification of adult worm (by tissue biopsy or ultrasound “filaria dance sign”)  
  - PCR

- **Presumptive diagnosis**
  - Compatible clinical picture + positive antifilarial antibodies
Lymphatic filariasis: diagnosis

Filaria Ab testing:

Thomas Nutman, M.D.
NIH
301-496-5398
Lymphatic filariasis: diagnosis

Circulating antigen detection
- Identifies patients \textit{actively} infected with \textit{W. bancrofti}
- 100% sensitive for patients with microfilaremia
- 100% specific
Lymphatic filariasis: treatment

- DEC (6 mg/kg/day for 12 days)
  - the regimen recommended by the CDC
  - has both microfilaricidal and macrofilaricidal activity
  - can reverse early lymphatic changes

Alternative regimens, including yearly single dose ivermectin+albendazole or DEC+albendazole are effective at decreasing microfilaremia, but not necessarily adults
Lymphatic filariasis: treatment
Importance of understanding etiology of filarial fevers

Acute filarial lymphangitis

Acute dermatolymphangioadenitis
Lymphatic filariasis: treatment
Importance of understanding etiology of filarial fevers

Acute filarial lymphangitis
inflammatory nodule w/descending lymphangitis
probably response to adult worms
Uncommon, only occurring in 3% of infected pts
THOUGH basically 100% of pts with LF have lymphangiectasia on bx.

Acute dermatolymphangioadenitis
→ ascending bacterial cellulitis or lymphangitis
Lymphatic filariasis: treatment

-- aggressively treating and preventing bacterial skin and soft tissue infections is paramount (Gerusa Dreyer)

\[ \Rightarrow \text{elevation, hygiene, foot care, treating cutaneous fungal infections, vigilance for bacterial infections} \]
Global Program to Eliminate LF (GPELF)

Biological considerations
→ organism doesn’t replicate in host
→ infection requires prolonged exposure

Technical considerations
→ treatment is very effective
→ monitoring tools excellent
→ cost is inexpensive
→ examples of successful eradication exist

GSK → donating albendazole
Merk → donating ivermectin
WHO, World Bank, CDC, UK, Japan, Arab Fund for Economic and Social Development, and many more countries and organizations

www.filariasis.org
Effects of anti-LF drugs: interruption of transmission

Diethylcarbamazine (DEC)

Albendazole (ALB)

Ivermectin (IVR)
Talk Outline

• Background on filarial infections
• Lymphatic Filariasis
• Onchocerciasis
• Loa loa
Onchocerciasis

• caused by *Onchocerca volvulus*

• a chronic, progressive disease

• **high morbidity**: eye, skin, lymphatic disease
• 120 million people at risk in 34 countries (99% in Africa)

• 18 million people infected (17M in Africa and 1M in South and Central America)
  → 4 million with skin manifestations
  → 2 million with blindness or severe visual impairment
Why is it called river blindness?
Why is it called river blindness?
Onchocerciasis

• Vector: *Simulium* spp. (blackflies)

• Adult worms: subcutaneous nodules
  • L3s undergo two molts over 6-12 months to become adults
  • males 2-5cm long, females 30-80cm long
  • males appear to migrate from nodule to nodule inseminating females
  • live 10-15 years

• Microfilariae: skin-dwelling
  • 300 microns long, live 6-24 months

• Animal reservoir: None
Clinical Manifestations in Chronic Infection

- Skin
  - nodules, pruritus, rash, depigmentation, lichenification, sowda

- Eye
  - keratitis, chorioretinitis

- Lymphatic obstruction
  - hanging groin, elephantiasis
Onchocercal nodule
Onchocercal dermatitis
Onchocercal dermatitis
Onchocercal dermatitis

- Peau d’orange
- Depigmentation
Onchocerciasis - Sowda
Onchocercal Eye Disease
Onchocerciasis – Punctate Keratitis
Onchocerciasis – Sclerosing Keratitis
Onchocerciasis – Hanging Groin
**Onchocerciasis: worm burden**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females per nodule</td>
<td>2-50</td>
</tr>
<tr>
<td>Males per nodule (always changing)</td>
<td>1-10</td>
</tr>
<tr>
<td>Microfilariae per female per day</td>
<td>1600</td>
</tr>
<tr>
<td>Daily microfilariae turnover</td>
<td>10,000-3,000,000</td>
</tr>
<tr>
<td>Total microfilariae in body</td>
<td>up to 150 million</td>
</tr>
</tbody>
</table>

*Udell D, Clinical Infectious Diseases 2007;44:53-60.*
Onchocerciasis: diagnosis

• Serology
  – anti-filarial
  – onchocerca-specific

• Parasitologic: skin snips, nodulectomy

• PCR of skin snips (increases sensitivity)

• Mazzotti test

• In development: urine antigen tests

Onchocerciasis: serology

- **Antifilarial IgG and IgG4 (anti-BmA)**
  - 100% sensitive
  - does not distinguish between the different filariae
  - Some cross-reactivity with other nematodes (ex. Strongyloides)

- **Onchocerca-specific (anti-Ov16)**
  - 80% sensitive
  - >98% specific for onchocerciasis
Onchocerciasis: skin snips
Onchocerciasis: nodulectomy
Onchocerciasis: Treatment

• Ivermectin → microfilaricidal, but does not kill adult worms

• 150 µg per kg orally given every 3-12 months to prevent blindness and decrease skin symptoms

• treatment should be continued in the setting of persistent symptoms, eosinophilia, parasitologic evidence of infection or continued exposure

• No effective prophylaxis is available
Is there something inside Onchocercal worms we can target in treatment?
Wolbachia

- Obligate intracellular bacteria

- Treatment with doxycycline for 6 weeks leads to disruptions of usual embryogenesis in adult worms for up to 18 months. Optimal duration/dose of doxycycline is under active study.

- NOTE: the corneal inflammation induced by Onchocerciasis may be due to an immune response against these bacteria.

Wolbachia

Ivermectin alone

Ivermectin + 6 weeks doxycycline

Targeting of Wolbachia is effective at treating Onchocerciasis
Targeting of Wolbachia is also effective in treating lymphatic filariasis

Macrolaricidal activity after doxycycline treatment of *Wuchereria bancrofti*: a double-blind, randomised placebo-controlled trial

Mark J Taylor, Williams H Makunde, Helen F McGarry, Joseph D Turner, Sabine Mand, Achim Hoerauf

8 weeks of doxycycline had significant effects on both microfilariae and adult worms
Talk Outline

• Background on filarial infections
• Lymphatic Filariasis
• Onchocerciasis
• Loa loa
Loiasis

- Vector: Chrysops spp. (deerfly)
- Host: human
- Microfilariae: blood-borne
- Adult worms: subcutaneous tissue
- Animal reservoir: None
Loiasis: epidemiology

Countries with reported cases
Loiiasis: clinical manifestations

- Asymptomatic microfilareemia
- Non-specific symptoms
  - fatigue, urticaria, arthralgias, myalgias
- Calabar swellings
- Eyeworm
- End organ complications (rare)
  - endomyocardial fibrosis, encephalopathy, renal failure
Calabar swelling
Loiasis: eyeworm
Loiasis in travelers

Symptoms at onset

- Calabar swelling: 40/41 (95%)
- Urticaria: 22/41 (54%)
- Myalagia/Arthalgia: 7/41 (17%)
- Eyeworm: 4/41 (10%)
- Asymptomatic: 8/41 (20%)
# Loiasis in travelers

<table>
<thead>
<tr>
<th>Laboratory findings at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microfilaremia</td>
</tr>
<tr>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Elevated IgE</td>
</tr>
<tr>
<td>Increased antifilarial IgG</td>
</tr>
<tr>
<td>Hematuria</td>
</tr>
</tbody>
</table>
Loiasis: Diagnosis

- **Definitive diagnosis**
  - Detection of microfilariae in daytime blood
    (Thick smear (insensitive), Saponin lysis, Knott’s concentration, Nuclepore filtration)
  - Identification of adult worm in the subconjunctiva or subcutaneous tissues
  - PCR blood

- **Presumptive diagnosis**
  - Compatible clinical picture + positive antifilarial antibodies
Loaisis: Treatment

- DEC → course results in clinical cure in 50% of patients

- Can repeat if necessary

- Can try albendazole
Ed Mitre
301-295-1958
emitre@usuhs.mil