Onchocerciasis, Loa Loa, Filariasis
A Case of the Creepy Crawlies

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Goals and Objectives

* Review Important Tissue Nematodes
  * Epidemiology
  * Clinical Findings
  * Diagnosis
  * Treatment
* Onchocerciasis, Loa Loa, Filariasis
  * Past, Present, Future
Nematode Biology

- **Prokaryotes**
  - Plants
  - Single-Cell (Protozoa)
    - “Gut Bugs”
      - ameba, giardia, etc
    - “Tissue Bugs”
      - kinetoplastids
    - “Blood Bugs”
      - plasmodia, babesia

- **Eukaryotes**
  - Fungi
  - Multi-Cell (Metazoan)
    - “Roundworms”
      - (nematodes)
    - “Tapeworms”
      - (cestodes)
    - “Flatworms”
      - (trematodes)
Nematodes = Roundworms

Macrofilariae = “adults”

Microfilariae = “babies”
Case Report

* 53 year old man from Sudan
* 20+ years of intensely pruritic skin, nodules on his rib cage, discoloration of some areas of skin, now with progressive vision problems
Case Report

* Onchocerciasis
Oncherciasis: Past

- “River Blindness”
- Blackfly lives and breeds near fast flowing streams and rivers
- Itchy/scaly skin with blindness was called “kru kru” or “craw craw”
- 1874: Microfilaria seen under microscope from skin snips by Irish naval surgeon John O’Neill
Onchocerciasis: Epidemiology

- 123 million people in endemic areas → 20 – 40 million people infected
  - 500,000 with secondary visual impairment, 270,000 blind
- HUGE increase during childhood
  - Hyperendemic area: 1-2% of kids <5 years old, 90% of kids 15 years old
- 99% of those infected live in Africa
  - Yemen, Venezuela, Brazil
- Worldwide, it is the second cause of infectious blindness
  - Trachoma is first
Onchocerciasis Epidemiology

WHO Distribution of onchocerciasis, worldwide, 2013
http://www.who.int/mediacentre/factsheets/onchocerciasis-map.png?ua=1
Onchocerca Volvulus Life Cycle

- Blackfly (genus Simulium) = intermediate host
- Humans = definitive host
- 5-stage life cycle
- Microfilariae persist in human host for 3-5 years
- Adult females live for 10-15 years
RIVER BLINDNESS
Onchocerciasis, also known as river blindness, is a parasitic disease caused by tiny worms or "microfilariae" and transmitted by flies. The disease affects an estimated 18 million people worldwide.

THE DISEASE CYCLE
2 Infection
The larvae enter the host's skin tissue, where they migrate and form nodules, and slowly mature into adult worms.

3 Proliferation
New worms form new nodules or find existing nodules and cluster together. Smaller male worms migrate between nodules to mate.

4 Reproduction
After mating, eggs form inside the female worm and develop into microfilariae. A female may produce 1,000 microfilariae per day.

5 Transport
When the infected host is bitten by another fly, microfilariae are transferred from the host to the fly.

Carter Center-Assisted Onchocerciasis Control Programs
Highlighted areas in Africa represent areas where The Carter Center is actively working. The highlighted areas in Latin America represent the 13 remaining foci.

DISEASE SYMPTOMS
Eye lesions
If microfilariae migrate to the eye, they can cause severe lesions and in some cases blindness.

Skin lesions
Many thousands of microfilariae migrate in the upper layers of the skin. When the microfilariae die, they cause skin rashes, lesions, intense itching and skin depigmentation.

Sources: World Health Organization, Centers for Disease Control; Map: The Carter Center
Larva drop from proboscis → human subcutaneous tissues → grow to adults (3-12 months) → female nematode makes fibrous capsule, males migrate → female sheds 100,000s microfilariae which migrate → microfilariae taken up by blackfly during meal → fly’s gut → muscles → grow to larva → proboscis
O. Volvulus: A Friend Indeed

- Wolbachia bacteria: BFF to many neotropical insects
- Endosymbiotic rickettsia-like bacterium required for survival of macrofilariae and for embryogenesis
Two Patterns of Presentation

- **African Savannah**
  - Ocular symptoms predominate
  - In hyperendemic areas, 80-100% have some vision symptoms by age 20, blindness by 40-50s

- **African Forest**
  - Skin symptoms predominate
  - 40% of patients older than 20 with “severe pruritus”
Onchocerciasis: Clinical Findings

- SKIN
- Papular dermatitis, intensely pruritic
  - TH1 Immune Response
- Chronic disease can develop asymptomatic depigmentation → Hypo vs Hyperpigmentation, “Leopard skin”
  - TH2 Immune response
- Lichenification, “Lizard skin,” “Elephant Skin”
- Eosinophilic response to onchocerca breakdown products
- Bacterial superinfection common
Onchocerciasis Skin Findings

Leopard Skin

Lizard/Elephant Skin
Onchocerciasis: Clinical Findings

* Skin Nodules: “Onchocercomata”
  * Subdermal nodules usually over bony prominences, “Robles Disease” in South America
  * Raised, round, firm, 2-3 cm, contain at least 1 adult
  * May be 1-100 per patient ("for each one you see, ~ 5 lie deeper").
  * Angiogenic protein produced by adult female
Onchocercomata
# Onchocercomata

Table 1. Illustrative numbers in onchocerciasis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females per nodule</td>
<td>2–50 worms&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Males per nodule (constantly exchanging)</td>
<td>1–10 worms&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Microfilariae produced per day per adult female</td>
<td>1600&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total body daily microfilariae turnover (steady state)</td>
<td>10,000–300,000&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total body loads</td>
<td>As high as 150 million microfilariae&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Females remain incarcerated in nodules [9].

<sup>b</sup> Males move in and out of nodules throughout lifespan [9].

<sup>c</sup> From [11].

<sup>d</sup> From [10, 12].
Lymphatics

- Lymphatic blockage may cause extremity edema, i.e. “equatorial arm”
- Lymphadenopathy: Regional or generalized
- Without treatment, lymphadenopathy will become chronic
  - Hanging Groin
- Scarred lymphatic channels can cause Elephantiasis-like syndrome
Onchocerciasis: Clinical Findings

- Ocular findings
- Anterior Disease: punctate or sclerosing keratitis, uveitis
- Posterior Disease: Chorioretinitis, optic atrophy
  - As microfilariae die, they release Wolbachia antigens as well
  - Immune reaction to antigens → corneal inflammation
    - Eventual scarring from years of repeated infections
  - Impaired vision starts by second decade
Onchocerciasis: Diagnosis

* Skin-snip
  * Small snip of skin (only dermis), place on slide with saline, microfilariae crawl out overnight into saline
  * 6 snips provide the most sensitivity, iliac crest, scapula, thigh, buttocks
  * Takes 1.5 years for mature worm to make enough microfilariae to make them detectable by this means
  * Low sensitivity of this testing (19-50%)
Onchocerciasis Skin Biopsy
Slit lamp of the anterior eye can show microfilariae or punctate keratitis, “snowflake” corneal lesions
  * Patients should sit with heads between legs for 5-10 minutes first
* New strategies: ELISA PCR tissue, Rapid serum antibody, Rapid urine antigen, finger prick whole blood O. Volvulus IgG4
  * Under development, only available in research labs
* Mazzotti reaction, no longer performed
  * Give 0.5-1mg/kg of Diethylcarbamazine
  * Kills microfilariae → within several hours develops maculopapular rash, fever, edema, pruritus, and HA
  * Can cause anaphylaxis and death
* DEC can also accelerate blindness
Oncho: Treatment

- Ivermectin (150ug/kg)
  - Kills microfilariae, but not macrofilariae, so it is not curative
  - Skin densities drop 85-95% by 2 months, back up to 20% by 1 year
  - Repeat treatments for the lifespan of the adult worm
    - Retreat every 6-12 months until asymptomatic
    - Remember, females live for 10-15 years!
  - Post-treatment reactions (edema, pruritus, backpain) decreases over time
- NOTE: Patient co-infected with LoaLoa can develop encephalopathy after Ivermectin
  - Rule out LoaLoa First! Ivermectin can cause fatal encephalopathy...
Onchocerciasis Treatment

* Suramin
  * Only approved medicine effective against adult worms, older drug
  * Injections BID for several weeks
  * Toxic though, so no longer used

* Moxidectin
  * Shown good effect against adult worms in animal studies, better safety profile in humans
  * Phase II Trials
Oncho Prevention

- Blackflies bite during the day, best prevention is to prevent getting bitten!
- DEET, long pants and long shirts
- APOC: Goal to eradicate Onchocerciasis from 23 nations by 2015 with Ivermectin for 90 million people
- Have already treated 68 million people, limited by conflict areas
Onchocerciasis: Doxycycline

- Doxycycline (100-200mg qday x 6 weeks) effectively kills the Wolbachia endosymbionts
- Pretreatment with Doxy, followed by Ivermectin resulted in 19 months of amicrofilaridermia, as well as 100% elimination of Wolbachia species from worms that were isolated
- Unclear safety of simultaneous Doxy + Ivermectin treatment, needs to be researched further for interactions
- CDC and RedBook say treatment with Doxycycline several days to one week after Ivermectin would be reasonable
Onchocerciasis: Future

- Onchocerca lupi, an emerging North American pathogen
- Canine and Feline parasitic infection, nodules in eyelid, sclera, conjunctiva
- 6 cases of human O. lupi infection reported from US, all traveled through SW
- Simulium black flies from Southern CA
- Skin nodules as well as 3 with nodules near cervical spinal canal

Otranto et al. Parasit Vectors (2015) 8:89  
Case Report

- 35 year old man, complaining of periodic swelling in his arms and legs
- Will last for several days, pruritic, edema, often with pain in nearby joints
- Then resolves
- Now with something wiggling in his field of view
Loa Loa
* 1778: Surgeon François Guyot noted worms in the eyes of West African slaves on a French ship to America; he successfully removed a worm from one man's eye
* 1890: Ophthalmologist Stephen McKenzie discovered microfilaria
* 1895: Scottish Ophthalmologist, Douglass Argyll-Robertson, Coastal Nigerian town of Calabar, localized edema of extremities noted
* 1910: Dr. Patrick Manson made connection from Loa Loa to Calabar Swellings
* 1912: British Parasitologist Robert Leiper discovered Chrysops species were the vector
Loa Loa: Epidemiology

- Limited to West and Central Africa
- Typically forest regions, also savannas
- Flies breed in the canopies of rainforests, more common in rainy season
- 14 million people live in areas of high endemicity
  - 20-40% of people have had a past infection
Loa Loa: Life Cycle

* Transmitted by Tabanid fly
* Genus Chrysops
  * Deerfly/Mango fly/Mangrove fly
  * Primarily Chrysops silacea and Chrysops dimidiata
Loa Loa: Life Cycle

Looks familiar...
Loa Loa: Life Cycle

- Microfilariae climb into dermis through hole cut in skin by fly
- Move on to lymphatics
- Adult worms set up shop in the tissue between the fascial layers of muscle and the skin
- Adult life span up to 17 years
- Once fertilized, females start releasing 10-20K microfilariae per day
- Microfilariae pass into the lymphatics → move to lung
- Some percentage continue on to peripheral blood
  - 17 months from penetration into skin to found blood
not all who wander are lost.
Loa Loa Life Cycle

- Microfilariae live for ~ 6-12 mos
- Diurnal periodicity: Densities of microfilariae peak by noon, and decrease to low levels at night
- Chrysops flies active in daytime

- Peripheral blood
- Urine
- Saliva
- Ascitic fluid
- Hydrocele fluid
- CSF (rare)
Loa Loa: Clinical presentation

* Asymptomatic ↔ Life-threatening complications
* First signs 5 months up to 13 years post-infection
* Calabar Swellings: Subcutaneous, non-pitting, non tender edemas
  * Limbs and forearms
  * Itching, decreased ROM at nearest joint, resolve after several days
  * Reappear at irregular intervals
* Hematuria, proteinuria, MPGN, Renal failure
* Cardiomyopathy
* Pulmonary infiltrates and pleural effusions
* Arthralgia (knees and wrists) and arthritis
Loa Loa: Clinical Findings

- Most specific sign is passage of adult worm under conjunctiva
- Can last for 30-60 minutes to more than 24 hours
  - Itching, photophobia, congestion of eye
  - Seen in 50% of people who live in hyperendemic areas
Loa Loa: Eye Worm
Loa Loa: Eye
Loa Loa: Diagnosis

- Eye worm = pathognomonic
- Often severe eosinophilia
- Giemsa-stain thick blood smear, often can see microfilariae “lashing about”
  - Collect during day (10am-2pm) given diurnal pattern
  - Quantify number of microfilariae per mL, guides treatment
- ELISA available in research labs, not clinically
- PCR that detects species-specific protein
  - 100% Specific, 95% sensitive
Diethycarbamazine: Treatment of choice
- Micro and macrofilariae, only option with both
- 8-10mg/kg/day divided TID x 21 days
- Typically takes 2-3 rounds for a definitive cure

BUT... Severe adverse events for patients with high microfilariae loads (ie >8000 microfilariae/mL)
- Itching, rash, edema, Headaches, fever in 50% of patients
- Encephalopathy most severe reaction, often fatal, unknown mechanism
**Loa Loa: Treatment**

- **Ivermectin** (Don’t use this when large burden!): Fatal encephalopathy
- **Albendazole**: Only micro, no macro
  - 200mg PO BID x 3 weeks
  - Goal to drop microfilariae counts <8000 microfilariae/mL prior to DEC treatment
- **Peace Corps Volunteer study** showed effective prophylaxis with DEC 300mg weekly
Loa Loa + Onchocerciasis Coinfection

* If you treat the Onchocerciasis with Ivermectin during high Loa Loa burden... fatal encephalopathy
* If you treat the Loa Loa with DEC during Onchocerciasis infection... Mazzotti reaction or accelerated blindness
* How frustrating!

**Proposed protocol**
1. Give Albendazole or Plasmapharesis to drop Loa Loa <8000mff/ml
2. Give Ivermectin (150-200ug/kg)
3. Give DEC of increasing doses over 3-4 weeks to max of 300-400mg/day
35 year old man who has had progressive swelling of his left leg for several years, now it is getting even bigger and more challenging to walk...
Can be found as early as 2000BC
- Pharoah Mentuhotep II
- Jan Huygen Linschoten 1588 in Goa
  - “Inhabitants were all born with one of their legs and one foot from the knee downwards as thick as an elephant’s leg.”
- Joseph Bancfort discovered adult worm
- 1877: Patrick Manson found mosquitoes were intermediate host
  - First time an arthropod was discovered to be a vector of disease
Filiariasis: Present

W. Bancrofti (90%)
Found throughout tropics

Brugia malayi
Only SE/East Asia

Brugia timori
Only Timor islands
Filiariasis: Epidemiology

- 120 million people infected
- 1 billion at risk
- 80 countries: but 70% of cases found in India, Nigeria, Bangladesh, and Indonesia
- Africa, South Asia, West Pacific Islands, South/Central America, Caribbean (Haiti and Dominican Republic)
- Men to women is 10:1, thought due to clothing
Filariasis: Life Cycle

Oh no... not again
Adult worms live in lymphatic vessels for 5-10 years
Microfilariae can live for up to 1.5 years
Mosquitoes: Aedes, anopheles, culex, or mansonia
Filariasis: Clinical Manifestations

* Asymptomatic (at least 50%)
  * Lymphatic dilatation and abnormal lymph flow without symptoms
  * Microscopic hematuria and proteinuria
  * Study with U/S showed ½ of adult men with asymptomatic microfilaraemia had nests of motile adult worms in their scrotal sacs

* Acute attacks
  * Episodic
  * Lymphadenitis, lymphangitis, fever and malaise

* Lymphadenopathy/Lymphedema
  * Adult worms blocking the lymphatics, inflammation very important to process
    * Inguinal, crural, axillary, intrascrotal lymphatic vessels
    * Can be seen in children
    * Legs, scrotum, penis, and arms
Elephantiasis
- Clinical feature, not synonymous
- Recurrent infections, inflammation and fibrosis
- Chronic skin infections from streptococcal species and fungal infections

Travelers
- Acute filarial lymphangitis
- 2-6 months after exposure
- Acute inflammation (usually leg, scrotum, or arm), progresses distally
- Indurated, tender, erythematous, resolves in 3-7 days

Filariasis: Clinical
Filariasis: Clinical Manifestations

- Tropical Pulmonary Eosinophilia (TPE)
  - Asthma-like symptoms
    - 1/3 of children with cough and wheeze had filarial infection, symptoms improved after treatment with DEC
  - Peripheral eosinophilia, elevated IgE, low grade fever, lymphadenopathy
  - Typically found in men 20-40 years old
- Chyluria
  - Passage of lymph in the urine so that it appears milky
W. bancrofti in Lymphatics
* Microfilariae on a thick blood smear
* Filtration of 1-5ml of blood with filter is more sensitive
* Highest blood specimen concentrations at night (10pm-4am)
* Distinguish the three species morphologically
* Children often negative
  * Assays to detect W. bancrofti antigen are available
Filarial Dance Sign
Diethylcarbamazine (DEC) is the drug of choice since 1947

- Microfilaricidal + Macrofilaricidal
- Single dose of 6mg/kg/day as effective as 12 day therapy per CDC
  - Use 14-21 days though for Tropical Pulmonary Eosinophilia (TPE)
- Cooking salt medicated with DEC has been used for mass treatment programs
- Severity of reaction to treatment is dependent on microfilarial density
  - Usually self limited
Filariasis: Treatment

- Ivermectin: microfilariae activity, but no macrofilariae activity
- Albendazole: macrofilariae activity, but no microfilariae activity
- Doxycycline: macrofilariae activity due to Wolbachia activity
- Some studies have shown DEC+Albendazole or Ivermectin + Albendazole is more effective than single drug therapy
  - WHO: Global Programme for Elimination of Lymphatic Filariasis
- DEC treatment would be problematic in patient with onchocerciasis (Mazzotti reaction, accelerated blindness) or high burden Loa loa (fatal encephalopathy)
  - Instead could use 400mg of Albendazole + 150ug/kg of Ivermectin
Filariasis Treatment

* Proper hygiene
* Skin care
* Treating skin lesions
* Exercise

Arrest Lymphedema Potentially Reverse
Filarial antigen test
   - Rapid
   - Simple enough to use in the field
   - Nearly immediate results
   - 100% sensitivity, 96% specificity

Some vaccine work underway using cloned filarial antigens
Questions?