Onchocerciasis
&
Lymphatic Filariasis

Global Health & Disasters Course
UCHSC

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Tissue Nematodes: Goals

• Refresh your understanding of important tissue nematodes in East Africa
  ✔ Epidemiology
  ✔ Clinical Presentation
  ✔ Diagnosis
  ✔ Treatment
  ✔ Control Strategies

• Interactive Please!
Prokaryotes

Plants

Eukaryotes

Fungi

Animals

Multi-Cell (Metazoa)

“Roundworms” (nematodes)

“Tapeworms” (cestodes)

“Flatworms” (trematodes)

Tissue Bugs
kinetoplastids

“Blood Bugs”
plasmodia, babesia

“Gut Bugs”
ameba, giardia, etc

“Tissue Bugs”
kinetoplastids

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ameba, giardia, etc
Nematode Groups

Tissue Nematodes
• Produce disease by migration of larvae through tissues of definitive host

Intestinal Nematodes
• Presence of adult worm in intestines responsible for major pathology
• Some have minor tissue phase
• Closely related animal parasites behave primarily as tissue nematodes in man.
Generic diagram of Male and Female Nematodes (Round worms)
A 55 y/o Ghanaian Grandfather

Years of intensely pruritic skin, loss of pigment at excoriation sites, gradual onset blindness.
Onchocerciasis

“River Blindness”
**Wuchereria & Brugia Life Cycle**

- Anthroponosis
- Vector borne
- Viviparous
- Adults harbor endosymbiotic Wolbachia bacteria
- Disease:
  - Adults clog & scar lymphatics
  - MF migrate through tissues

Microfilaria

- Sheathed: $230-320 \times 10 \mu m$
- Tail pointed, free from nuclei

- Invasion
- Maturation time 2-3 weeks
- May survive several months

Mosquito

Nocturnal periodicity

**Development in mosquito**
The larvae penetrate stomach, migrate to thoracic muscles, develop, then migrate to head, mature and now infective

**Localization**

**Repair**
Onchocerciasis: Epidemiology

A Plague Across the Tropics
Similium fly
“Black Fly”
“Buffalo Gnat”

Larvae mature in fast-running water

A “low-Efficiency” Vector (Average exposure ~ 1 year to infection)
Onchocerciasis: Transmission

Two Main Patterns in Africa

West African Savanna: Anterior Ocular Disease Predominates
• Hyperendemic regions: 80-100% have eye disease by age 20
• Blindness peaks in 40’s – 50’s

African Forests: Skin Disease Predominates
• 42% of pts > age 20 report severe pruritus
• Eye manifestations rarer, more likely posterior
Onchocerciasis: Transmission

Two Main Patterns in Africa

Possible there are two strains of O. volvulus?

West African isolates carry greater quantity of endosymbiotic Wolbachia DNA... Genetic comparisons of worm ongoing.
Onchocerciasis: Presentation

Systemic

- Musculoskeletal Pain
- Arthralgias
- Backache
- Weight loss

... All non-specific
Onchocerciasis: Presentation

Skin

Texture / Color Changes

- Lichenification (“Lizard Skin”)
- Hyper- or Hypo-Pigmentation (“Leopard Skin”)
- Microfilariae cause both by chronic, unrelenting excoriation due to eosinophilic inflammation (Th-2) with migration, leading to pruritus
- Erysipelas-like raised, spongy, dark plaques sometimes seen early in course due to acute inflammation (“Sowda”)
- Bacterial superinfection common
Onchocercarial Dermatitis
“Leopard Skin”
Onchocerciasis: “Elephant” or “Lizard” skin and papulodermatitis

**DDX:**
- “Norwegian” scabies in HIV+
- Severe Contact Dermatitis
Onchocerciasis: Presentation

Skin

Nodules

• Raised, round, firm, 2-3 cm diameter.
• Fixed in place by a fibrous capsule.
• May be 1-100 per patient (“for each one you see, ~ 5 lie deeper”).
• Each harbors $\geq 1$ adult worm… less pruritic
• Location related to vector’s biting habits
  (1) Africa – Bony Prominences & Head
  (2) Americas – Upper Trunk & Head
Onchocerccoma (Nodule)
Onchocerciasis: Presentation

Lymphatics

• Lymphatic blockage may cause extremity edema ("equatorial arm"), reminiscent of calabar swellings of Loiiasis
• Regional or generalized LAN common
• Without treatment, LAN will become chronic, may become dependent ("hanging groins")
• Scarred lymphatic channels may lead to elephantiasis-like syndrome
Onchocercic lymphadenopathy

“Hanging Groin”
Onchocerciasis: Presentation

Eye

- Pathogenesis: *Microfilarial* migration and inflammation.
- Any part of the eye may be affected
- Anterior disease (punctate or sclerosing keratitis, uveitis) more common with savanna transmission
- Posterior disease (chorioretinitis, optic atrophy) more common with forest transmission
- Any of these may cause vision loss
Onchocerciasis:
Blindness with Corneal Opacification
Onchocerciasis: Optic Atrophy and Sclerosing Keratitis
Onchocerciasis: Retinal atrophy
**Onchocerciasis: Diagnosis**

Clinical Suspicion, plus...

Skin biopsy

- Snips quick, easy, remarkably painless
- Microfilariae crawl out of snips overnight into saline, seen by microscope next day
- Adults in excised nodule
- Slit lamp of eye: characteristic corneal disease
- Eosinophilia (often > 3,000 cells / microliter)
Onchocerciasis: Diagnosis

Clinical Suspicion, plus...

- Skin biopsy
  - Snips quick, easy, “remarkably painless”
  - Down to dermis only (bloodless)
  - 2-6 snips (pelvic girdle, buttocks, external thigh)
  - Pathologist will see microfilariae on fixed section....

- If you have no pathologist, drop specimen into saline; mf will crawl out of snips overnight, can be seen by microscope next day
Onchocerciasis: Skin Biopsy, microfilarium
Microfilarium from skin snip

Unsheathed mf,
No nuclei in tail... thus
Onchocerca volvulus
Onchocerciasis: *Diagnosis*

Clinical Suspicion, plus…

- Skin biopsy
- Adults in Excised Nodule (with mf seen in the interstitium, unlike Loaisis where the mf are released into the bloodstream)
Onchocerciasis: Biopsy of a nodule with adult worms
Onchocerciasis: *Diagnosis*

Clinical Suspicion, plus...

- Skin biopsy
- Adults in Excised Nodule
- Slit Lamp Exam

✓ Characteristic punctate keratitis, or even live mf (pt should sit forward for 2 min first to enhance detection of mf)
Onchocerciasis: *Diagnosis*

Clinical Suspicion, plus…

- Skin biopsy
- Adults in Excised Nodule
- Slit Lamp Exam
- DEC Patch Test… Rarely used anymore

✓ 10-20% Diethylcarbamidine solution applied to skin… positive if robust dermatitis reaction

✓ NPV and PPV unclear, but has been used for screening when snips not available
Onchocerciasis: Diagnosis

Clinical Suspicion, plus...

Mazzotti Test NOT PERFORMED!

PO DEC and high infection burden:
• Rapid mf killing
• Extreme pruritus
• Possible angioedema, anaphylaxis, patient death!

• PCR great PPV, NPV less helpful, and test is virtually unavailable
Onchocerciasis: Treatment

• Ivermectin 150mg PO Q 3-6 months

Caveat: Loa Loa Co-infection!

• Ivermectin kills Loa mf, not adults.
• Onchocerca death may facilitate adult Loa penetration into CNS.
• Test for Loa in advance, or treat with doxy alone vs. doxy + albendazole
Onchocerciasis: Treatment

- Ivermectin 150mg PO Q 3-6 months
- Doxycycline 100-200mg PO Daily x 6 weeks, followed by Ivermectin
  - Targets symbiotic Wolbachia
  - May sterilize female adult worms, enhance reduction in mf birth
  - Need for ongoing dosing make this impractical in endemic areas
**Onchocerciasis: Treatment**

- Ivermectin 150mg PO Q 3-6 months
- Doxycycline 100-200mg PO Daily x 6 weeks, followed by Ivermectin
- Future options may include moxidectin and closantel
- Nodule excision for symptomatic or cosmetic relief… has been proposed for head lesions, to reduce mf proximity to eyes
Onchocerciasis: Prevention

- Ivermectin Mass Periodic Treatment
  - Public pressure, embarrassment, public good… the story of Merck’s ivermectin donation program

  APOC: Goal to eradicate oncho from 23 nations by 2015 with ivermectin for 90 million people

  - Already treated 68 million… conflict limits coverage efforts

- Vector Control (larva-eating fish)
Onchocerciasis: Key Concepts

- **Onchocerca volvulus** infection via simulium fly
  - Savanna areas: Eye pathology predominates
  - Forest areas: Skin pathology predominates

- **Diagnosis**: Skin snips, slit lamp

- **Rx**: Goal: reduce symptoms, prevent blindness
  - Ivermectin to reduce mf release
  - Doxycycline to kill wolbachia
  - Watch out for Loa Loa Co-Infection

- **Prevention**: Periodic Mass Ivermectin Dosing

- **Future**: Better drugs?
CHANGED PRIORITIES AHEAD
Loa Loa: Humans alone are NOT ENOUGH to complete life cycle (as usual)!
Loiiasis: Epidemiology

A West & Central African Specialist

- 3-13 million infections
- Occult infections make case finding problematic
- Incidence rises with age
- Years of exposure usually, but may happen in mere weeks (rare among travelers)
- Up to 40% of communities may be infected
Loa loa Vector: Chrysops fly ("Tabanid fly family") ("Deer fly") ("Horse fly")

Breeds in forest canopy... lays eggs in swamps
Loiasis: *Pathophysiology*

- *Adults* migrate through sub-cutaneous tissue, wandering restlessly.
- (Contrast with *O. volvulus* adults living sedentary life in dermis nodules)
- *Loa adult* migration leads to symptoms
- Mothers give birth with live mf into bloodstream, but mf *not* thought to cause symptoms
Loiiasis: Presentation

Asymptomatic

• Many in endemic areas go for years, or forever, without symptoms
• Ongoing inoculation with mf may induce immune tolerance
Loiasis: *Presentation*

- **Eye**
  - Adult crawling under bulbar conjunctivae
  - A frequent initial presentation
  - Great alarm to the pt...
  - Modest conjunctival inflammation...
  - Not sight-threatening
  - Often there for only minutes!
Loiiasis: Presentation

Extremities

• “Calabar Swellings:” Unilateral, transient edema of an arm or leg, or discrete 5-20 cm nodules
• Presumed due to angioedema in response to adult migration or birth of mf
• Usually last days (can be hours to weeks)
• Adult worms may induce intense eosinophilic inflammation of joint or nerve compartments
Loiasis: *Presentation*

**Systemic**

- Chronic fatigue reported among travelers… which has resolved with adult extraction
- Eosinophilia may be more prominent among travelers than endemic patients…
- *Rare* complications include:
  - Hypereosinophilic cardiomyopathy
  - Immune-complex mediated nephropathy
  - Inflammatory encephalitis (esp. post-DEC)
Loiasis: Diagnosis

- Eye Migration Pathognomonic
- Adults have been biopsied from calabar swellings...
- Microfilaremia in *diurnal* pattern
Loa loa: Microfilarium in blood

Sheathed mf, nuclei extend to tip of tail
Loiasis: Diagnosis

- Eye Migration Pathognomonic
- Adults have been biopsied from calabar swellings...
- Microfilaremia in diurnal pattern
- Serology best with IgG4… but poor PPV in endemic populations (cannot distinguish “active” vs prior infection)
- Eosinophilia not reliable among endemic populations (only 50% will have elevated counts)
Loiiasis: Treatment

Loiiasis usually harmless!

Treatment not usually necessary!
Loiasis: Treatment

Surgery

- Careful extraction from the eye may please the patient…
- May only be visible for minutes!
- \textbf{Not} necessary for sight preservation
- Surgical removal from soft tissues is challenging because of difficulty locating the worm
- PET Scan, anyone…?
Loa loa: extraction from eye and tail of adult male
Loa loa worm extracted from skin

DO NOT RECOMMEND THIS
Loiasis: Treatment

Diethylcarbamazine (DEC)

- Active against mf and adults
  ✓ Rapidly kills mf
  ✓ ~30% Adults die
- Relapse Rate ~50%... *Repeat* treatment if symptoms recur
Diethylcarbamazine (DEC)

- **Pitfall**: Paradoxical worsening with sudden antigen exposure due to mass mf death by DEC
- May cause Jarisch-Herxheimer type reaction (anaphylaxis, shock) or encephalitis
Loiiasis: Treatment

Diethylcarbamazine (DEC)

- **Pitfall:** Paradoxical worsening with sudden antigen exposure due to mass mf death by DEC

- **Solution:** Quantify microfilaremia
  
  ✓ If < 2,500 mf/ ml blood, treat with DEC
  
  ✓ If > 2,500 mf / ml blood, consider no treatment if asymptomatic, or prednisolone 1 mg / kg / day x 3 days at start of therapy
Loiiasis: Treatment

DEC Dosing: Many regimens published!

• 6 mg/kg PO x 1 dose (CDC)
• 6 mg/kg PO QD x 12 days (Medical Letter)
• 8-10 mg/kg PO QD x 21 days (old standby)
• Graded Dosing
  ✓ Day 1: 50 mg (1 mg/kg)
  ✓ Day 2: 50 mg (1 mg/kg) TID
  ✓ Day 3: 100 mg (1 to 2 mg/kg) TID
  ✓ Day 4 to 21: 9 mg/kg in three divided doses

• Followup: Regardless of regimen chosen, repeat if symptoms recur
Loiiasis: Treatment

**DEC Alternatives**

- Albendazole 400 mg/kg PO QD x 3 days
- or
- Ivermectin 400 micrograms/kg PO x 1 dose

- Much less effective against mf, only “stuns” the adults
- Possibly better for high mf loads (gentler killing effect, slower mf drop)

- **Followup**: Regardless of regimen chosen, repeat if symptoms recur
Loiiasis: Prevention

- Bed nets of little value, as chrysops bites during the day
- Vector control difficult to implement
- Routine suppressive treatment with DEC safe and effective at reducing transmission; currently in place for LF, side benefit of reducing loiasis
Loiiasis: Key Concepts

• *Loa loa* worm infection via chrysops fly
  ✓ *Central & West Africa*

• *Presentation*: Adults in eye, Calabar swellings

• *Diagnosis*: Daytime blood films

• *Rx*:
  ✓ DEC… but quantify microfilaremia, Rx prednisolone if > 2,500 / ml
  ✓ Surgical extraction if opportunity arises…

• *Prevention*: Periodic DEC for endemic areas

• *Future*: Better drugs? Better fly control?
Ah, there's nothing more exciting than science. You get all the fun of sitting still, being quiet, writing down numbers, paying attention. Science has it all.
A 51 y/o Nigerian Farmer

Years of progressive scrotal and left leg edema.
Several related disorders
Caused by threadlike worms of superfamily FILARIOIDEA
Inhabit lymphatics, subcutaneous and deep tissues
Produce acute inflammation, chronic scarring and lymphatic obstruction
Filarial Lifecycle

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

Human Stages:
1. Mosquito takes a blood meal (L3 larvae enter skin)
2. Adults in lymphatics
3. Adults produce sheathed microfilariae that migrate into lymph and blood channels
4. Mosquito takes a blood meal (ingests microfilariae)

= Infective Stage
= Diagnostic Stage

CDC
http://www.dpd.cdc.gov/dpdx
Culex quinquefasciatus: One Vector of Lymphatic Filariasis

- Happy to breed in stagnant water anywhere… including urban areas
- LF: Not limited to rural Africa
Heterogeneous Vectors

- Numerous mosquito genera and species have been documented as vectors, including Culex, Anopheles, Aedes
- Vectors vary by location… and thus so does daily timing of peak risk, and perhaps location of body parts affected
- *W. bancrofti* in Africa: Transmitted primarily by nocturnal feeding patterns
Filariasis: Epidemiology

A Global Phenomenon

- Warm climates 41°N to 30°S
- Both urban and rural transmission
- Many skip areas
- WHO: 200-250 million people infected

- *W. bancrofti* in Africa: 40-90 million infected
Asymptomatic Microfilaremia

- As with Oncho and Loa, many infected will have *no symptoms* with mf in the bloodstream
- Diagnosis in these cases usually made during routine screening
- But, even when asymptomatic, pts often have lymphatic changes (e.g. scrotal lymphangectasia)
Filariasis: Presentation

Acute Adenolymphangitis

Adult Worms Responsible for Disease

- Fever & Rigors
- Lymphangitis and Lymphadenopathy
  - Regional, e.g. one entire extremity becomes inflamed and edematous
  - Edema is soft and pitting
  - Thrombophlebitis may follow
  - If scrotal involvement, epididymitis and acute scrotum may develop
Acute Dermatolymphangioadenitis

*Adult Worms* still probably responsible, but with likely *bacterial superinfection and / or acute allergic response*

- Fever, Rigors, myalgias, prostration
- Lymphangitis and Lymphadenopathy
  - Sharply demarcated, raised, indurated, hyperpigmented, warm, edematous plaques
  - Antecedent skin breach, wounds, trauma common

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**Filariasis: Presentation**
Filariasis: Presentation

Chronic Lymphatic Obstruction

*Adult Worms* Responsible for Disease

- Relatively rare manifestation, likely dependent on adult worm burden
- Disruption of lymphatic channels due to mechanical blockage, inflammation, scarring
- Dependent brawny, firm edema, in extreme cases elephantiasis (painful, debilitating, associated with bacterial superinfection)
- Dilated lymphatics may erode into ureters, causing chyluria (and even malnutrition)
Unilateral, persistent, progressive lower extremity edema ("Elephantiasis")
Genital involvement is variable, but strikes more often in Bancroftian filariasis.
Wucheria bancrofti in dilated lymphatic channel
Lymphogram: Dilated, tortuous channels, and calcifications
Chyluria

• Retroperitoneal lymphatics erode into ureters

• Voided urine has milky appearance, due to fat micelles in chyle

• Intermittent, often worst after rising in the morning

• May worsen following fatty meals
Ultrasonographic appearance of Adults in Scrotum:
Fliarial Dance Sign
Tropical Pulmonary Eosinophilia

- MF may be responsible for disease, as they are cleared by host inflammatory response
- Paroxysmal nocturnal cough, wheezing, low-grade fever, fatigue
- Eosinophilia > 3,000, increased bronchovascular marking on CXR, very high anti-filarial antibody and IgE levels (may lead to pulmonary fibrosis without treatment)
Tropical Pulmonary Eosinophilia

Differential Diagnosis

• Loeffler’s Syndrome
• Asthma
• Idiopathic hypereosinophilic syndrome
• Allergic bronchopulmonary aspergillosis
• Drug allergy
• Other helminth infections (during pulmonary migration)
Filariasis: Diagnosis

Nocturnal Blood Films (22:00 – 02:00)

• Fine to start with finger prick… may need up to 1 ml blood to make dx if routine smear is negative
• Concentrate via nucleopore filter or centrifugation
• Heavily infected pts may have > 10,000 mf / ml blood!

Sheathed mf,
No nuclei in tail… thus Wuchereria bancrofti

10,000 mf / ml blood!
Brugia: Sheathed Microfilarium, Two Terminal Nuclei
Blood Films Rule
✓ Cheap, fast, easy, quantitate, speciate
Antigen testing performs very well... if you can perform it!
✓ WHO: Qualitative card immunochromatographic test
✓ Og4C3 ELISA: 99% sensitivity, thus excellent NPV, but PPV lower to determine active disease, as antigen may persist for many months post-Rx
Ultrasound May Help Too!
“Classic Filarial Dance Sign.”
Filariasis: Treatment

For Public health…. DEC!

Many regimens published

- 6 mg/kg PO QD x 12 days (Medical Letter)
- 6 mg/kg PO x 1 dose (CDC)

✓ Yields 90-99% mf reduction at one year follow up!
For the Individual Patient

- Pre-Treat with Doxy 100mg PO BID x 4 weeks (to kill endosymbiotic wolbachia), then single dose of DEC 6 mg/kg PO x 1
- Enhanced durability of reduction in mf
- Not practical for mass administration
**Filariasis: Treatment**

**DEC Alternatives**
- Albendazole 400 mg/kg PO QD x 3 days
- Kills adults, not mf’s… thus more gradual decrease in microfilaremia
- Good alternative for those who cannot tolerate DEC (rare) or may be co-infected with Oncho (not so rare)

**PLUS**
- Ivermectin 150 micrograms/kg PO x 1 dose
- Kills mf, not adults, thus repeat doses will be necessary
Filariasis: Treatment

Beyond Medications

- *Hydrocele Drainage*: Provides temporary relief, but will reaccumulate
- *Surgery*: Tricky, skilled hands and appropriate centers are challenging to find
- *Nigerian experience*: No complications in 301 hydrocelectomies, apparent benefit (Thomas NJTMH 2009).
Filariasis: Treatment

Beyond Medications

Supportive Care:

- Wash with soap & water twice daily
- Prompt care of superficial cuts and abrasions, including use of topical abx ointment
- Elevate affected body part at night
- Keep fingernails and toenails clean
- Wear shoes
Filariasis: Prevention

- Mosquito Control Where Feasible (especially peri-domestic)!
- Mass DEC Administration
  - Safe & Well Tolerated
  - If continued locally for 5-6 years, may drop microfilaremia below levels necessary for infection to continue
  - Success claimed / documented in China and S. Korea
  - Tablets Q 6-12 months, or added to table salt!
Filariasis: Key Concepts

• *Wuchereria bancrofti* infection via mosquitoes
  ✓ Across the Tropics, including urban areas

• Presentation:
  ✓ Acute adenolymphangitis / dermatitis
  ✓ Chronic elephantiasis / chyluria
  ✓ Tropical pulmonary eosinophilia

• Diagnosis: Nighttime blood films or ag test

• Rx:
  ✓ DEC… or ivermectin + albendazole if Oncho risk
  ✓ Edema care, prevent superinfections

• Prevention: Periodic mass DEC administration
Tissue Nematodes: Key Concepts

• **Onchocerciasis (river blindness):** *Onchocerca volvulus*
  – Vector: blackflies (*Simulium* spp.): Africa, C/S America
  – Eosinophilia, nodules, skin changes, microfilariae in eye and skin, blindness
  – Dx: Skin snips, serology, Mazzotti reaction
  – Rx: Ivermectin every six months

• **Loaiasis:** *Loa loa*
  – Transmitted by deer flies (*Chrysops*): West / Central Africa
  – Conjunctival or dermal migration (Calabar Swellings)
  – Dx: Blood microfilaria in day, demonstration of adult, or serology
  – Rx: DEC (or Ivermectin + albendazole if Oncho risk)

• **Lymphatic filariasis (elephantiasis):** *Wuchereria & Brugia*
  – Vector: mosquitos (often night biting): much of the tropics
  – Clinical: nocturnal fevers, pulmonary symptoms, retrograde lymphangitis, lymphedema
  – Dx: Blood microfilaria at night or after DEC
  – Rx: DEC (or ivermectin if Oncho risk)