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

Eukaryotes

Plants

Fungi

Animals

Multi-Cell (Metazoan)

“Roundworms” (nematodes)

“Tapeworms” (cestodes)

“Flatworms” (trematodes)

“Gut Bugs”

ameba, giardia, etc

“Tissue Bugs”

kinetoplastids

“Blood Bugs”

plasmodia, babesia

Roundworms

(nematodes)

Tapeworms

(cestodes)

Flatworms

(trematodes)
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”
Onchocerca volvulus Life Cycle

1. Blackfly (genus *Simulium*) takes a blood meal (L3 larvae enter bite wound)
2. Subcutaneous tissues
3. Adults in subcutaneous nodule
4. Adults produce unsheathed microfilariae that typically are found in skin and in lymphatics of connective tissues, but also occasionally in peripheral blood, urine, and sputum.
5. Blackfly takes a blood meal (ingests microfilariae)
6. Microfilariae penetrate blackfly’s midgut and migrate to thoracic muscles
7. L1 larvae
8. L3 larvae
9. Migrate to head and blackfly’s proboscis

I = Infective stage
D = Diagnostic stage
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
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
Onchocercocoma (Nodule)
Onchocercomas (Nodules)
Onchocerciasis: Presentation

Lymphatics

- Lymphatic blockage may cause extremity edema ("equatorial arm"), reminiscent of calabar swellings of Loiisisis
- 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 Loa asis 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
Loiasis: Presentation

Asymptomatic

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

- Adult crawling under bulbar conjunctivae—a frequent initial presentation
- Great alarm to the pt… and modest conjunctival inflammation… but not sight-threatening
- Often there for only minutes!
Loiasis: 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 inflammatory joint or nerve compartments
Loiiasis: 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)
Loiasis: Treatment

Loiasis usually harmless!

Treatment not usually necessary!
Loiasis: Treatment

Surgery

- Careful extraction from the eye may please the patient…
- May only be visible for minutes!
- 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
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 for 3 days at start of therapy
Loiasis: 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
Loiasis: 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
Loiisis: 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
**Loiasis: 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.
Filariasis: Definition

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

Human Stages:
1. Infective Stage
2. 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 from 41N to 30S
- 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
Filariasis: *Presentation*

**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
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.
Wuchereria 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)
- 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
Filariasis: Diagnosis

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!
Filariasis: Treatment

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)