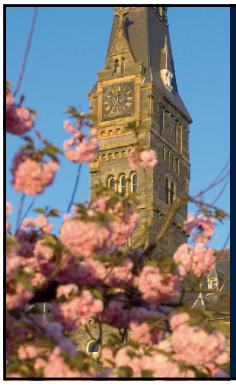


"It's All in the Head":

CNS infections from the Tropics

Dr. Adrienne Showler

Director of Tropical Medicine, Georgetown University Hospital

Attending Physician, Clinical Parasitology Section, NIAID, NIH

GEORGETOWN UNIVERSITY

1

Objectives

1. Review **differential diagnosis** for Central Nervous System lesions in patients from tropical regions
   - Cystic lesions
   - Ring-enhancing lesions

2. Discuss **diagnosis and management** of 2 specific causes of CNS disease

2

General Considerations:

- Epidemiology: consider the exposure history
- Host: are they immunocompromised (or could they be?)
- Time course
- Pattern on imaging
- Anything we can look for outside the CNS ?
  - Serologies ?
  - Other organ systems ?

3

Case 1: 30-year-old Woman from **Angola** with **Headaches & Seizures**

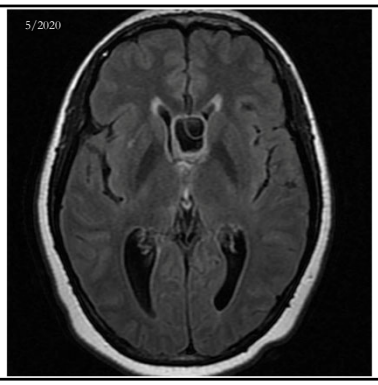
2005
Age 15: Seizure at night
Treated x 3 months in South Africa with unknown medication

2010–2012
Headaches: episodic, lasting several days, associated with photophobia
CT head "normal"
Diagnosed with migraines

Moved to United States (age 20)
2010

Age 30: 3 weeks severe headaches
2 days fever at outset, resolved
Headaches resolved with amitriptyline
Mar. 2020

4



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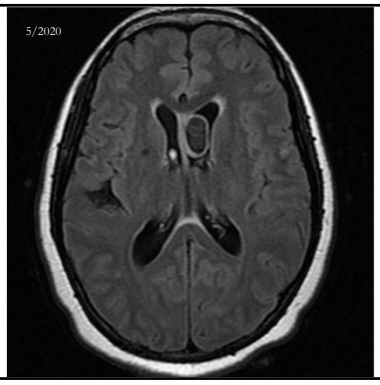

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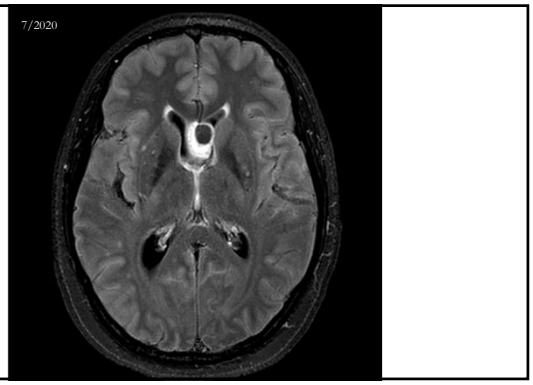

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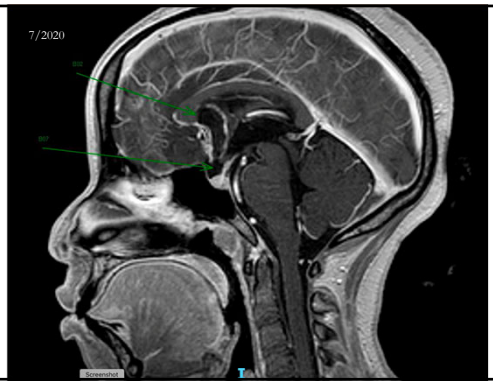

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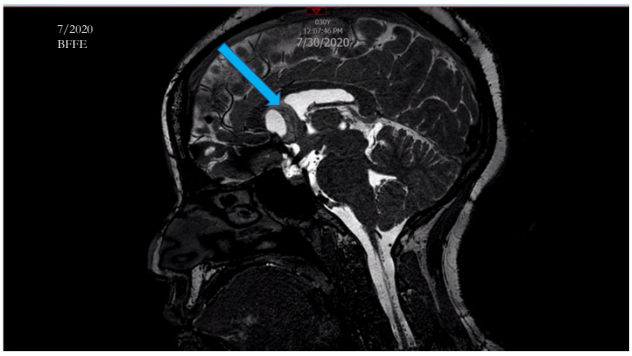


9

Cystic Lesions in the Brain Differential Diagnosis

Common
Neurocysticercosis
Brain abscess

Rare
CNS Echinococcus
Coenurosis

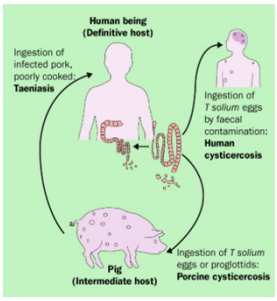
Non-infectious
Arachnoid cyst
Epidermoid cysts
Pilocytic astrocytoma
Glioblastoma
Metastasis

10

Cysticercosis = Larval form of Taenia solium

Taeniasis

- Definitive host
- Eat undercooked pork
- Tapeworm in human intestine
- Shed eggs in stool

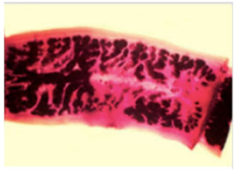


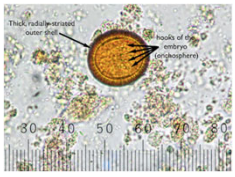
Cysticercosis

- Intermediate host
- Eat eggs from human tapeworm carrier
- Larvae encyst in human organs

Garcia. Lancet 2003; 362: 547–556

11

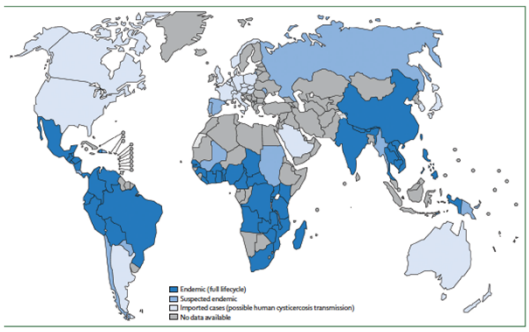




Taeniasis: Eggs and proglottids passed in stool

Garcia. Lancet Neurol 2014; 13: 1202–15; Bobby Pritt. Parasite Wonders

12



Garcia. Lancet Neurol 2014; 13: 1202–15

13

Step 1: Location, Stage, Number

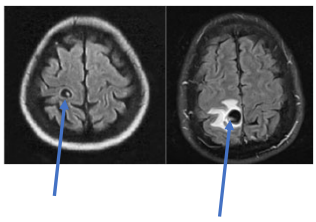
Parenchymal	Viable
Ventricular	Degenerating
Subarachnoid	Calcified
Spinal	
Ocular	

14

Parenchymal Disease: What we are most familiar with

Typical lesions:
- < 2cm (with exceptions)
- thin wall
- smooth, circular border
- Scolex

Main presentation:
- Seizures



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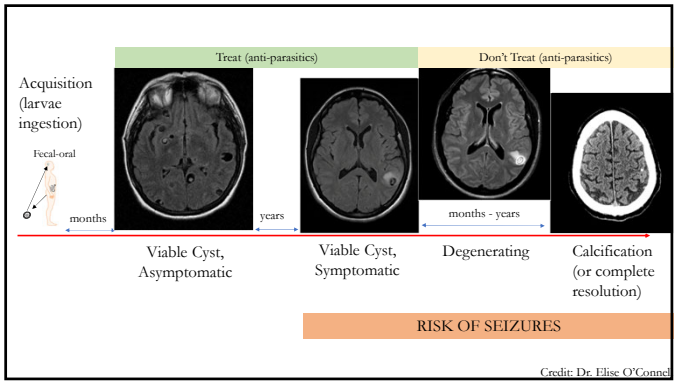
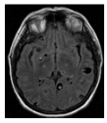


16

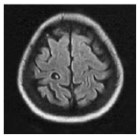
Diagnosing Parenchymal Disease

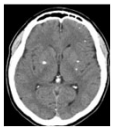
Sensitivity of serology EITB (enzyme-linked immunotransfer blot, CDC)

>1 viable parenchymal lesion:
Sensitivity close to 100%



1 lesion: sensitivity ~50%





Once calcified serology often becomes negative

17

Treating Parenchymal Disease

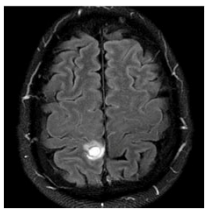
1. Antiepileptics

2. Steroids

3. Antiparasitics

1-2 viable cysts: albendazole (10-14 days)
- Kills cysts faster than the natural progression
- **Decreases generalized seizures** compared to no treatment

>2 viable cyst: albendazole + praziquantel (10-14 days)
- praziquantel and albendazole (68%) vs. albendazole alone (5-25%)



18

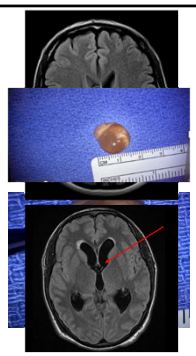
You Cannot Kill what is Already Dead

Treatment: Antiepileptics alone

19

Ventricular NCC

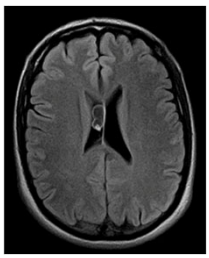
- **Surgery when possible**
  - No antiparasitics needed
  ***if those are the only cysts
- **Medical treatment sometimes needed**
  - Location difficult to access
  - Cyst adhered to ventricular wall
- **Be aware if treating medically**:
  - Risk "entrapping" ventricle due to inflammatory response



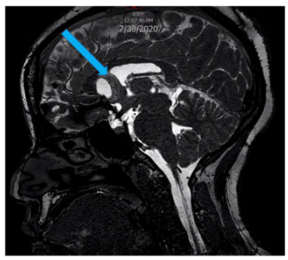
Images: Dr. Benjamin Tack

20

Our Case: Initially Appeared Ventricular, but It's NOT



Ventricular cyst

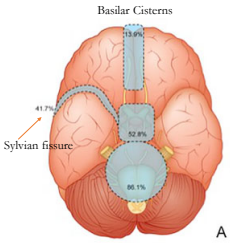


30-year-old woman from Angola

21

Subarachnoid NCC (aka. Racemose)

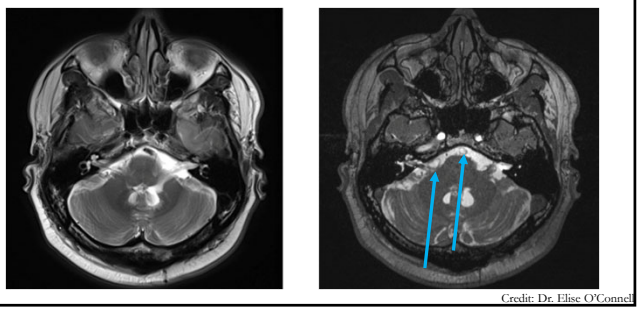
- Chronic proliferative form
- "Racemose" = bunch of grapes
- Cysts can be as large as they want
- Longer incubation period (10-20 years after exposure)



Bazan R et al. 2016 PLoS NTD

22

Type of Imaging Matters
BFFE, FIESTA, 3D CISS



Credit: Dr. Elise O'Connell

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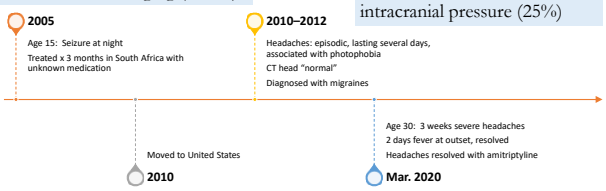
Clinical Presentation of SANCC

History of seizures or calcifications on imaging (~50%)

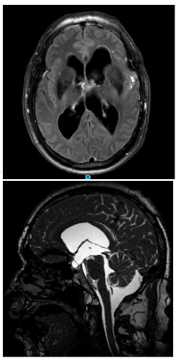
Headaches without increased intracranial pressure (25%)



Aseptic meningitis (20%)

24

Hydrocephalus is Common: 50-60%

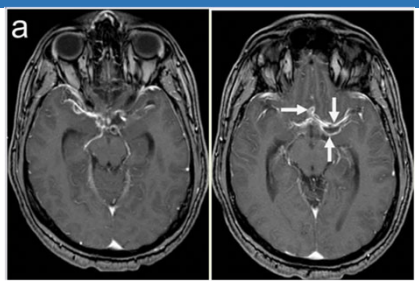


- Communicating—chronic inflammation causing meningeal scarring
- Obstructive—due to intraventricular cysts/debris causing obstruction

Fix it first before you treat !!

25

Arachnoiditis causes Lacunar infarcts



Nash. Curr Opin Infect Dis. 2020 October ; 33(5): 339–346

26

Complications at the time of diagnosis

TABLE 3
Complications

Complication	Number (%)
Hydrocephalus	19/34 (55.9)
Shunt	14/34 (41.2)
Ventriculostomy	1/34 (2.9)
Spinal pain symptoms	5/34 (14.7)
Infarct (%, median, range)	6/34 (17.6, 3, 1–6)

Nash. Am. J. Trop. Med. Hyg., 102(1), 2020, pp. 78–89

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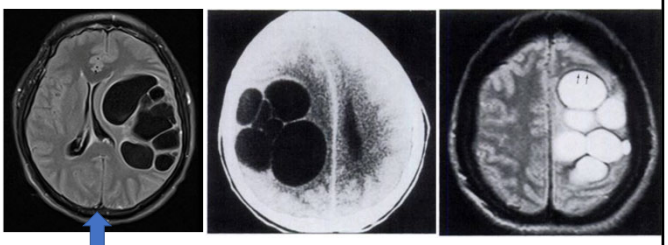
Other presentations: Giant Cyst



Subarachnoid NCC

Echinococcus

Tuzun M and Hekimoglu B. 1998. AJR. "Hydatid Disease of the CNS: Imaging Features"

28

Case 1: 30-year-old woman from Angola w/ SANCC

Cysticercosis EITB (CDC): Positive
Serum *T. solium* qPCR: 37.9 (+)

EITB sensitivity ~100% for subarachnoid NCC

Lumbar puncture:
- 12 WBCs (97% lymphocytes)
- N protein (26 mg/dL)
- N glucose

CSF pleocytosis
- Lymphocytes or eosinophils

29

Case 1: 30-year-old woman from Angola w/ SANCC

Spinal MRI: No evidence of cysticercosis involvement

40-60% with basilar disease also have spinal disease

MRI complete spine should be done in all cases of SANCC

Fundoscopy:
No intraocular cysticerci

Check before antiparasitics, all patients (not just subarachnoid)

30

Preparing for treatment: Screen for coinfections (you're about to start high dose steroids)

Our patient

- Strongyloides IgG negative
- **Hep B Sag +**
- HIV negative
- IGRA negative
- T. cruzi IgG (if co-endemic area, not here)

31

SANCC Treatment

30-year-old from Angola

- If there is hydrocephalus, fix it first (shunt or ventriculostomy)

- **Start high dose steroids**
  - Taper Slowly

Dexamethasone 6 mg PO BID
- + PJP prophylaxis
- + entecavir (Hep B)

- **Albendazole + praziquantel**
  - Mean treatment: 9-12 months

Albendazole 400 mg BID
+
Praziquantel 1800 mg BID

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Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Diagnosis and Treatment of Neurocysticercosis: 2017 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH)[1]

A. Clinton White Jr,[1] Christina M. Coyle,[2] Vedantam Rajshekhar,[3] Gagandeep Singh,[4] W. Allen Hauser,[5] Aaron Mohanty,[1] Hector H. Garcia,[6] and Theodore E. Nash[7]

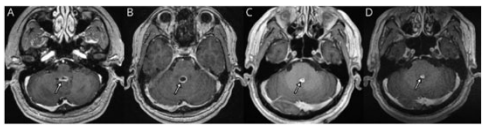
[1]University of Texas Medical Branch, Galveston; [2]Albert Einstein College of Medicine, Bronx, New York; [3]Christian Medical College, Vellore, and [4]Dayanand Medical College, Ludhiana, India; [5]Columbia University, New York, New York; [6]Instituto Nacional de Ciencias Neurologicas and Universidad Peruana Cayetano Heredia, Lima, Peru; and [7]National Institutes of Health, Bethesda, Maryland

39. We suggest that antiparasitic therapy be continued until there is radiologic resolution of viable cysticerci on MRI and resolution of other evidence of cysticerci (*weak, low*). Responses often require prolonged therapy, which can last for more than a year.

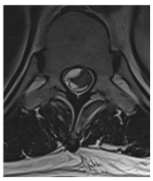
33

Imaging in isolation not always a reliable indicator of cure or relapse

Persistent imaging findings are common, even with successful treatment



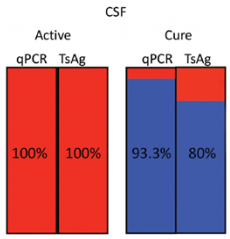
2 years anthelmintics with cure



Sanchez Bokuarte.Neurol Clin Pract. 2025;15:e200553.

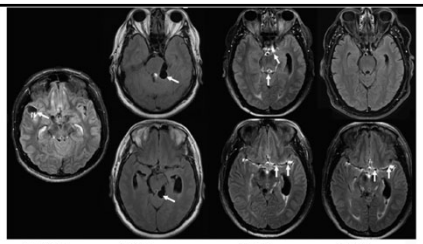
34

Negative CSF *T. solium* qPCR predicts cure (ventricular and subarachnoid)



O'Connell et al. 2020. CID

35



	Pre-clinical	Stage 1	Stage 2	Stage 3
	Asymptomatic cystic proliferation, no obvious inflammation	Classic Racemose: Basilar cisterns and Sylvian fissure involvement of fluid-filled cystic masses, limited inflammation. Mass effect predominates	Arachnoiditis: Inflammation predominates with a spectrum of cyst damage or no discernible cyts	Cure: Decreased but persistent inflammation. Calcification and scarring seen
Parasite viability	+++	+++	+/-	-
TsAg and qPCR positivity	+/-	+++	+	-

Nash. Curr Opin Infect Dis. 2020

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Post-treatment status

Status	Number/total (%)
Well without sequelae	14/33 (42.4)
Lost to follow-up	1/34 (2.9)
Unresolved infection	1/33 (3.0)
Residual hydrocephalus	2/33 (6.0)
Mild intellectual impairment	5/33 (15.2)
Unable to work*	8/33 (24.2)
Visual impairment	3/33 (9.1)
Episodic neurological symptoms	8/33 (24.2)
Neurological sequelae from stroke	2/33 (6.0)
Depression	4/33 (12.1)
Seizures	2/33 (6.0)
Headaches	2/33 (6.0)
Poor balance/walking	3/33 (9.1)
Focal neurological weakness	4/33 (12.1)
Aseptic necrosis	8/33 (24.2)
Secondary CNS pathology	2/33 (6.0)
Basilar artery aneurysm	1/33 (3.0)

Nash. Am. J. Trop. Med. Hyg., 102(1), 2020, pp. 78–89

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CASE 1: Subarachnoid Neurocysticercosis -RECAP-

- **Be Suspicious: Endemic area + CNS cystic lesions**
  - "Arachnoid cysts", "epidermoid cysts", "CSF loculations"
  - Unexplained hydrocephalus, aseptic meningitis
- **Get the right imaging:** MRI w/ BFFE, FIESTA or 3D CISS
- **Pressure and inflammation take priority**
  - Fix hydrocephalus first
  - Start steroids and control symptoms first, taper slowly
- **SANCC: prolonged antiparasitics** (albendazole + praziquantel)
  - Imaging alone not a reliable predictor of cure
  - Negative T. solium qPCR from CSF indicative of cure

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Case 2: **Altered Mental Status from Honduras**

49-year-old woman, unknown past medical history

Symptoms: 3 weeks altered mental status, headache, right-sided weakness

Travel History: Born in Honduras, now living in Texas, USA

Examination: Afebrile, altered mental status, 3/5 power (Right side)

Laboratory Work Up: HIV+, CD4 38, VL 375,000 copies

Credit: Dr. Eva Clark (Baylor)
Yasukawa et al. Am J Trop Med Hyg. 2014 Jul;91(1):84-5. PMID: 24891470.

39

*Representative image (another case)

40

Differential diagnosis, Ring Enhancing Lesions in patient with advanced HIV

Most common:
Toxoplasmosis
CNS lymphoma

Other considerations:
Pyogenic abscess (including Nocardia, brucella)
Tuberculoma
Cryptococcoma
Fungal abscess (aspergillus, dimorphic fungi)
Cysticercosis (degenerating)
Metastatic tumour

Something else …

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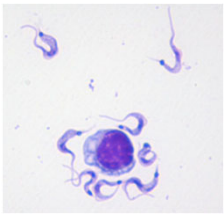
Lumbar Puncture

CSF
- 3 WBC
- 1 RBC
- Protein 78 mg/dL
- Glucose 55 mg/dL
- Gram stain negative
- Cryptococcal antigen negative

Blood
- T. cruzi serology pos (IFA & EIA)
- T. cruzi PCR positive in blood (and CSF)
- ECG and TTE normal



T. Cruzi trypomastigotes in cerebrospinal fluid (CSF) (Giemsa stain, 1,000)

Yasukawa et al. Am J Trop Med Hyg. 2014 Jul;91(1):84-5. PMID: 24891470.

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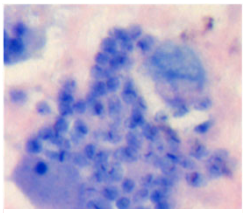
Outside brain biopsy re-reviewed



T. cruzi amastigotes with rod-shaped kinetoplasts in glial cells (Giemsa stain, 1,000)

Chagasic meningoencephalitis
CNS Chagoma

T. Cruzi reactivation in advanced HIV

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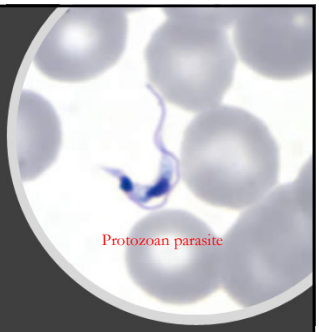
Chagas Disease

a/k/a American Trypanosomiasis
a/k/a T. cruzi

- Vector-borne (Reduvid Bug)
- Mother-to-child (vertical transmission)
- Blood transfusion
- Organ transplantation
- Ingestion (acai, sugarcane)



Protozoan parasite

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Where have you lived?

45

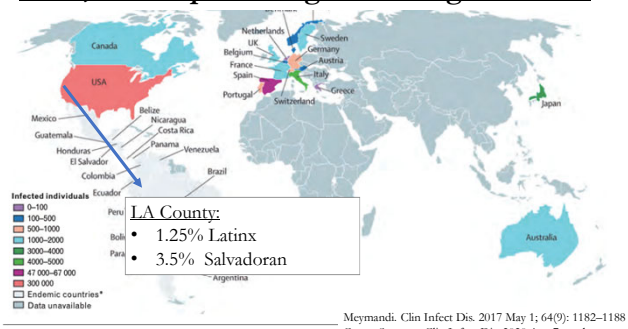
Endemic in 21 Countries in Latin America

- 7 million infected worldwide
- 100 million live in at-risk region
- 7 in 10 not diagnosed

Meymandi. Clin Infect Dis. 2017 May 1; 64(9): 1182–1188

46

~300,000 People Living with Chagas in USA



LA County:
- 1.25% Latinx
- 3.5% Salvadoran

Meymandi. Clin Infect Dis. 2017 May 1; 64(9): 1182–1188
Castro-Sesquen. Clin Infect Dis. 2020 Aug 7; epub

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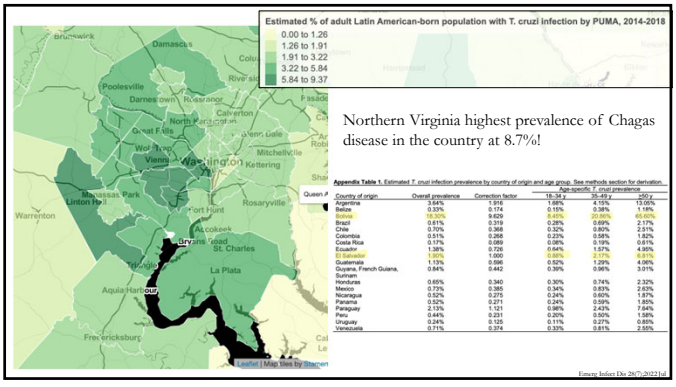

Northern Virginia highest prevalence of Chagas disease in the country at 8.7%!

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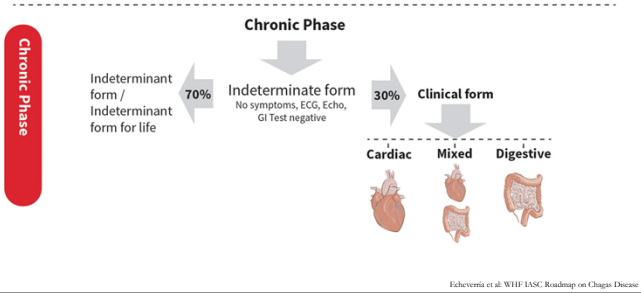
Chronic Chagas is (mostly) What We See in USA



Echeverría et al: WHF IASC Roadmap on Chagas Disease

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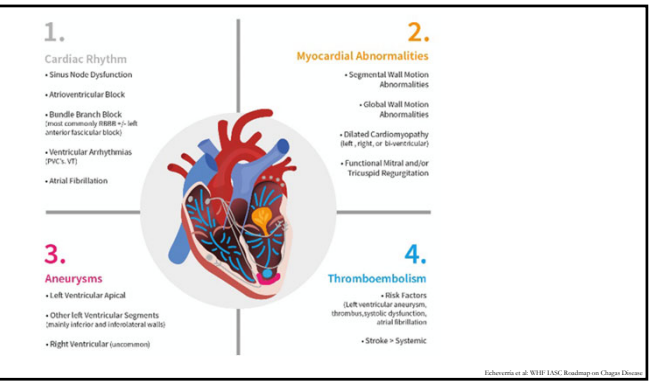

Echeverría et al: WHF IASC Roadmap on Chagas Disease

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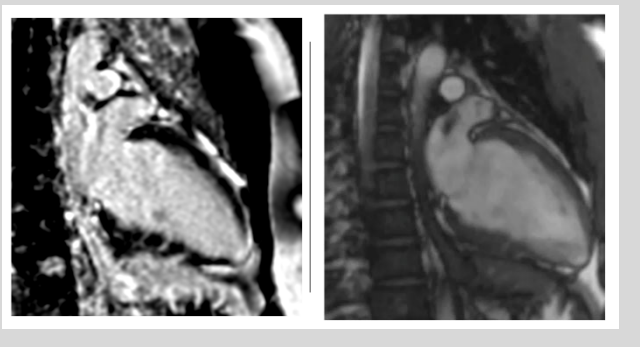

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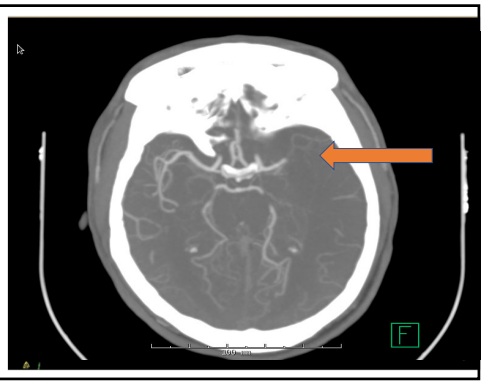
Two Years Later . . .

- Large left MCA stroke
- Acute right-sided weakness, aphasia



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How to diagnose CHRONIC Chagas: Serology x 2 !

Test	Antigen	Availability
Hemagen ELISA	Purified antigens from parasite culture	Commercial
InBios Chagas Detect Plus	Recombinant multiepitope fusion antigen	Point of care - Lateral flow assay
Ortho *T. cruzi* ELISA	Purified antigens from parasite culture	Blood bank only
Wiener Chagatest ELISA recombinante v0.3.0	Recombinant trypomastigote-shed acute-phase antigens	Commercial
Immunoblot	Trypomastigote Excreted-Secreted Antigen (TESA)	United States Centers for Disease Control

*** Serology may be negative in patients with advanced HIV**

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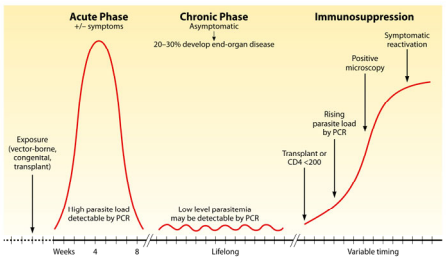
Back to Case 2: What happens when a patient with chronic Chagas disease **becomes immunosuppressed?**



Clark et al. Clin Microbiol Rev. 2024

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T. cruzi reactivation in advanced HIV

- "Opportunistic infection" – CD4 typically < 100
- Cumulative incidence if not on antiretrovirals: 15-20%
- **Meningencephalitis** is most common presentation
  - Easily mistaken for toxoplasmosis
- Mortality with symptomatic disease >75%

Clark et al. Clin Microbiol Rev. 2024

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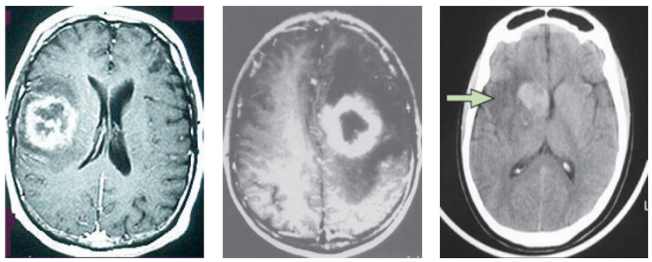

Most common presentation: single or multiple ring-enhancing lesions

Di Lorenzo. Journal of neuroimaging 1996.

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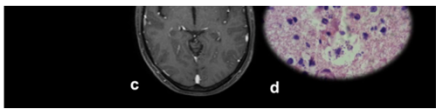
SHORT REPORT

"Bunch of acai berries sign": a new radiological sign in patients with CNS involvement in Chagas disease

Ana Paula Alves Fonseca[1,2,3] · Rodolfo Ferreira Queiroz de Melo[2,4] · Tereza Menezes[4] · Cândida Maria Alves Soares[4] · Vanille Rodrigues[4] · Ronnie Peterson Marcondes Alves[5] · Rita de Cassia Maciel Pincerato[2] · Federico Roca[6] · Antonio José da Rocha[1,3]



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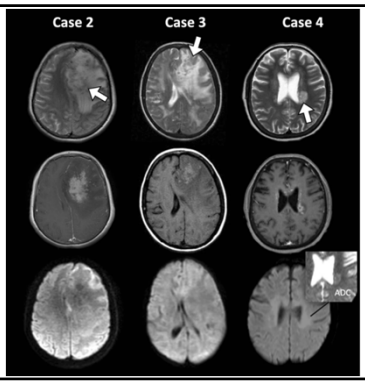

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CNS T. cruzi

- Suspect when neurologic symptoms or abnormal CNS imaging
- MRI more sensitive than CT
- **Up to 15% have normal MRI and CT head**
- Typical LP:
  - **mild CSF pleocytosis (<100 cells/mL), lymphocytic**
  - **High protein**
  - **Low glucose**

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T. cruzi Reactivation: Diagnosis

- *T. cruzi trypomastigotes* on microscopy

- Clinical manifestations of reactivation
  - myocarditis, fever of unknown origin, panniculitis, **meningoencephalitis**
    + *T. cruzi* in tissue or **cerebral spinal fluid (PCR or microscopy)**
- Rising blood parasite load on **serial qPCR**, or very high parasite load

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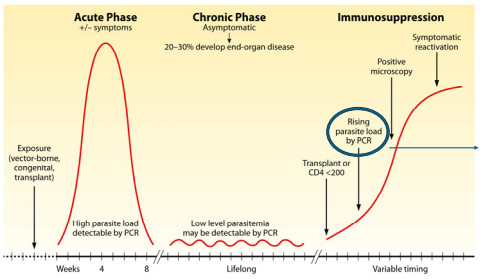

Post-transplant

- Monitor serial qPCR
- Pre-emptive treatment if rising

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Monitoring Post-Transplant Prevents Complications

Months post-transplant	PCR and microscopy
0-2	Weekly
3	q2 weeks
4-6	Monthly
>6 months	Consider (net state immunosuppression)
Additional testing as needed:	Unexplained febrile episode Increase in immunosuppressive regimen

Kransdorf. Curr Opin Infect Dis. 2014 Oct;27(5):418-24.
https://optn.transplant.hrsa.gov/media/1169/chagas_disease_04-2015.pdf

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Management: *T. cruzi* reactivation in HIV

Antitrypanosomal medications	Benznidazole 5 mg/kg/day for 60 days *Nifurtimox if benznidazole not available
Restore immune function!	Start antiretrovirals No reports of IRIS
Consider secondary prophylaxis	Benznidazole 5 mg/kg MWF Until CD4 >200

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Benznidazole Basics

- Total: 5-8 mg/kg/day
  - Cap at 300 mg/day (150 mg q12h)
- WITH food
- NO alcohol (+ 3 days after stopping)
- Teratogenic (pregnancy test, birth control)

- Check-in, CBC, Creatine, liver enzymes q2-3 weeks
  - Agranulocytosis
  - Hepatitis

- I don't give patient the full supply of medication

View of the 100-mg tablet.

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Case 3 – CNS Chagas Disease Continued

- Received benznidazole for 60 days
- Mental status gradually improved, but weakness persisted
- MRI on day 14 after showed decrease in lesion size
- Antiretroviral started day 17
- 5 months after diagnosis doing well, CD4 359, VL <200 copies

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Which HIV Positive Patients Need Chagas Screening ?

One or more risk factors? (Ranked in importance)

1. Born in or lived >6 months in an endemic country (Mexico, Central or South America)
2. Having a family member with CD
3. Lived in housing made of natural materials (mud, adobe, thatch, palm leaves) in Mexico, Central or South America
4. Being bitten by kissing bugs or finding kissing bugs in the home (Conditional recommendation, low quality evidence)

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CASE 2: T. cruzi Meningoencephalitis in a patient with HIV -RECAP-

- HIV Positive Patients with risk factors for T. cruzi should be **screened (2 different serologies)**
- **Meningoencephalitis** is most common form of reactivation in advanced HIV, and has a high mortality
- **Reactivation diagnosed differently – use qPCR**
- T. cruzi reactivation: **Antiparasitics are an emergency**

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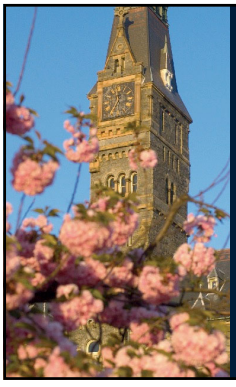

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Dr. Eva Clark (Baylor)
Georgetown University Infectious Disease

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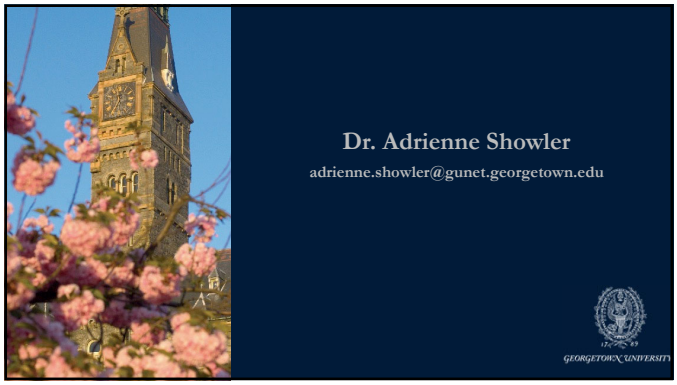
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