Parasitic infection

of the CNS

Thanawan Tiraweerakhajorn, MD

Contents

Introduction

- The neurological, cognitive, and mental health problems caused by these parasitic infections affect in low- and middle-income countries; however, sporadic cases also occur in nonendemic areas because of an increase in international travel and immunosuppression caused by post-transplantation therapy or HIV infection.
- Long-term immunosuppression caused by medications such as prednisone might also increase the risk for acquiring parasitic infections.

Classification

Protozoan Infections

Cerebral Amebiasis
Cerebral Malaria
Toxoplasmosis
Trypanosomiasis
American Trypanosomiasis (Chagas' Disease)
African Trypanosomiasis (Sleeping Sickness)

Nematode Infections

Angiostrongyliasis
Gnathostomiasis
Strongyloidiasis
Toxocariasis
Trichinellosis

Trematode Infections

Paragonimiasis
Schistosomiasis

Cestode Infections

Cysticercosis
Echinococcosis (Hydatid Disease)
Coenurosis
Sparganosis

Pathogenesis of parasitic CNS infection

Neurotropic" parasites enter the central nervous system (CNS) via..

- blood-brain barrier
- blood-CSF barrier

Parasite, parasite products, host inflammatory response

Neuroinflammation

Induce neurological damage

Pathophysiology of parasitic CNS infection

Primary role of neuroinflammation

- To protect the CNS from insults, including invasion and attack by infectious agents.
- Neuroinflammation facilitates the opening of physical barriers, or when the pathogen develops Trojan horse strategies by using activated cells to enter the brain.
- Inside the brain, pathogens are difficult to dislodge and cause CNS dysfunctions.

intracellular Toxoplasma

extracellular African trypanosomes

Postan M and Pattenberg ME (2021) Editorial: Neurotropism of Parasites and the Immune Response. Front. Immunol. 12:775066

Postan M and Rottenberg ME (2021) Editorial: Neurotropism of Parasites and the Immune Responses. Front. Immunol. 12:775666.

Pathophysiology of parasitic CNS infection

Toxoplasma gondii

- Toxoplasma to spread into the CNS, and parasite specific T cell mediated immune responses control but do not eradicate the infection

- Affect neurons, astrocytes and microglia

.

Trypanosoma brucei

- T. brucei circulating in the bloodstream can attack the CVOs and choroid plexus, providing a route for brain penetration.

- From the choroid plexus to the ventricles and initiate accelerated infiltration of T cells and parasites in periventricular areas.

- Crossing the border into the BBB-protected hypothalamic arcuate nuclei → affects sleep/wake behavior.

Plasmodium

- Cause severe alterations and inflammation in the brain vasculature, without entering the brain parenchyma

- Innate immunity recognizes various parasite-derived molecules by brain endothelial cells innate immune receptors mediates their activation, and trigger inflammatory responses that lead to microcirculatory and coagulation disturbances and to altered vascular permeability impairing BBB integrity.

Tenia solium

- Invade the CNS via hematogenous spread of larval stages to small vessels, by in situ deposition or embolism of eggs following anomalous migration of adult worms to the CNS, attaching to the nasal neuroepithelium and penetration via the olfactory nerve pathway, or directly invading the neural skull and intervertebral foramina.

Clinical manifestation

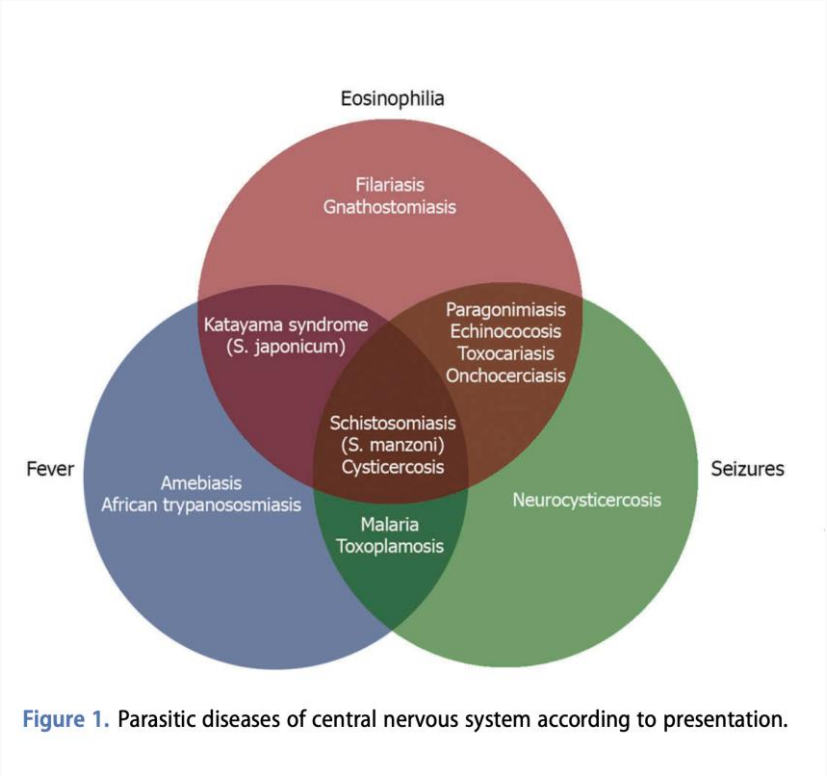


Figure 1. Parasitic diseases of central nervous system according to presentation.

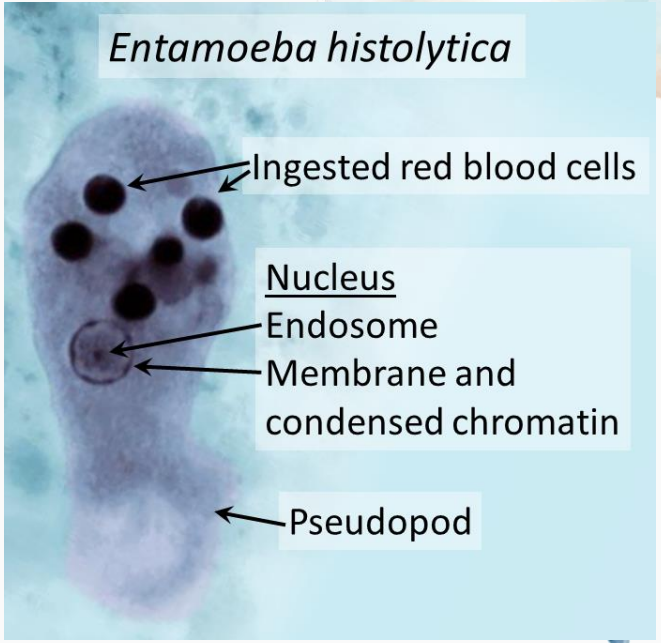
Variety of lesions, including granulomatous or cystic lesions, abscesses, encephalitis, meningitis, or myelitis, any of which may occur alone or in combination.

EXPERT REVIEW OF NEUROTHERAPEUTICS, 2016 VOL. 16, NO. 4, 401–414

Table of contents

Amebiasis (*Entamoeba histolytica*)

- Presents regions with inadequate sanitation
- Endemic areas in Africa, Asia, and Latin America
- *E. histolytica* as the third most common pathogen among travelers returning with infectious gastrointestinal disease, accounting for 12.5% of confirmed cases and an estimated incidence of 14 cases per 1000 returning travelers.
- Asia, Europe, North America, and Australia, specific populations, including gays, bisexuals, and other men who have sex with men (MSM), are identified as being at higher risk.
- In Europe, often linked to travel, immigration, have been reports of brain abscesses caused by *E. histolytica* from Turkey and Spain.



Amebiasis (*Entamoeba histolytica*)

Pathogenesis

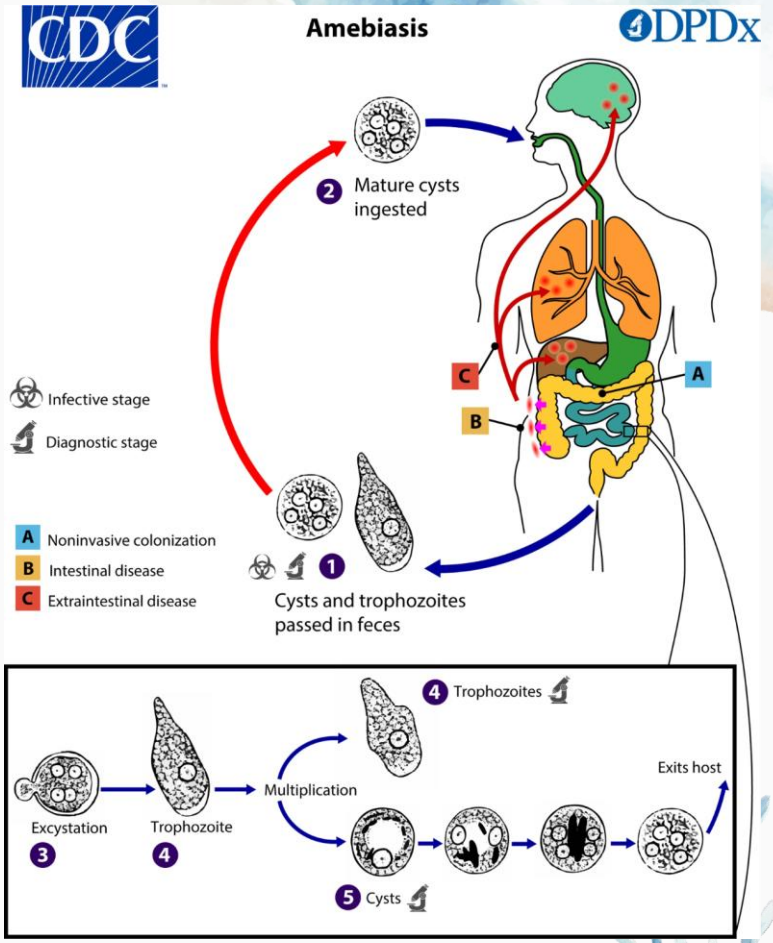
- Trophozoites originating from the intestines→ hematogenous spread → brain
- By adhering to endothelial cells and overcoming the blood–brain barrier, these trophozoites infiltrate brain tissue.
- Subsequent immune responses elicit inflammation and tissue damage.
- Formation of pus-filled abscesses within the brain

Clinical manifestations: severe headaches, fever, seizures, and neurological deficits.

Identification of *E. histolytica* trophozoites in brain tissue samples, obtained via biopsy or surgical drainage, confirms the diagnosis

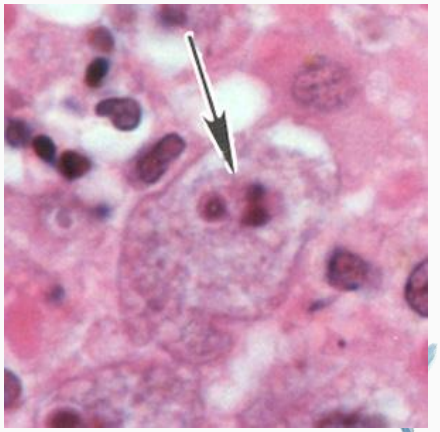
Management

- Combined pharmacological + surgical intervention if needed.
- Metronidazole, coupled with other antibiotics



Morán, P. et al. Amoebiasis: Advances in Diagnosis, Treatment, Immunology Features and the Interaction with the Intestinal Ecosystem. *Int. J. Mol. Sci.* **2023**, *24*, 11755.

Free living Amebiasis



3 genuses of free-living amoeba, *Naegleria*, *Acanthamoeba*, and *Balamuthia*

- *Naegleria fowleri* infections occur in healthy individuals; most often acquired during swimming in warm freshwater
- *Acanthamoeba* spp. and *Balamuthia mandrillaris* are opportunistic pathogens, typically affecting immunocompromised hosts.

Pathogenesis

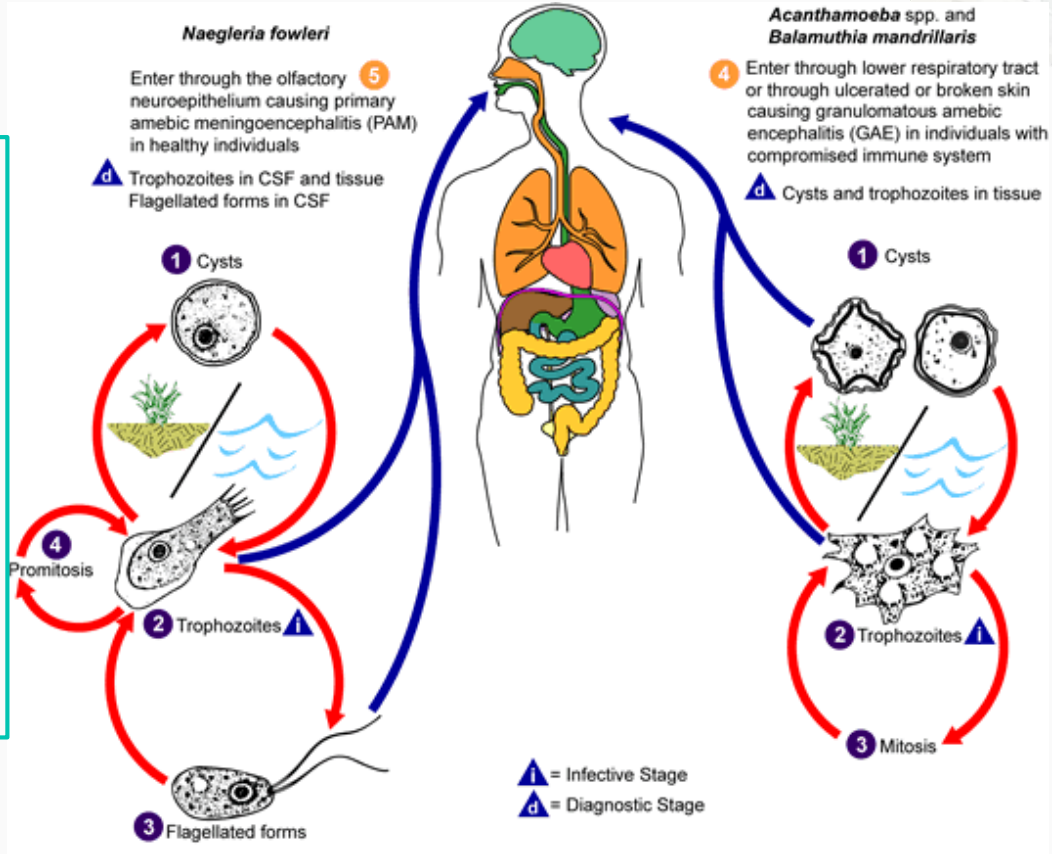
- *N. fowleri* invades the olfactory neuroepithelium in the nasal mucosa and penetrates the brain via the subarachnoid space.
- *Acanthamoeba* spp. and *B. mandrillaris* enter the human body through the skin or the upper respiratory tract and secondarily invade the CNS by the hematogenous route

Morán, P. et al. Amoebiasis: Advances in Diagnosis, Treatment, Immunology Features and the Interaction with the Intestinal Ecosystem. *Int. J. Mol. Sci.* **2023**, 24, 11755.

primary amoebic meningoencephalitis

- Hemorrhagic necrosis of the brain parenchyma that is more prominent around the olfactory bulbs and frontal lobes

- Neuroimaging studies of nonspecific brain swelling and the diagnosis must be confirmed by the demonstration of mobile trophozoites in fresh cerebrospinal fluid (CSF)



CDC

Granulomatous amoebic encephalitis

- Subacute disease characterized by fever, focal neurological signs, seizures, increased intracranial pressure, and behavioral changes.

- Formation of hemorrhagic parenchymal brain abscesses that are seen on neuroimaging studies as multiple ring-enhancing lesions surrounded by edema.

- Invasion of the walls of intracranial arteries by trophozoites causes a necrotizing angiitis lead to ischemic strokes.

- Diagnosis requires the

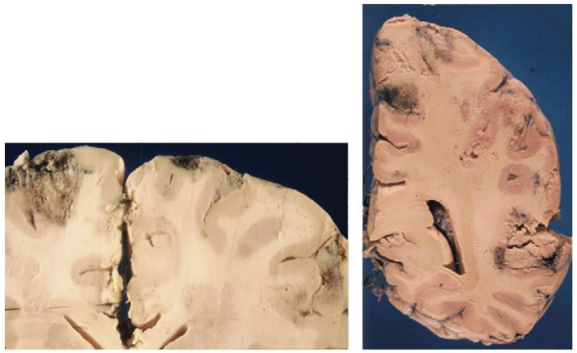


Fig. 5.13. Granulomatous amebic encephalitis. Multiple necrotic and hemorrhagic nodules in cerebral cortex and subcortical white matter.

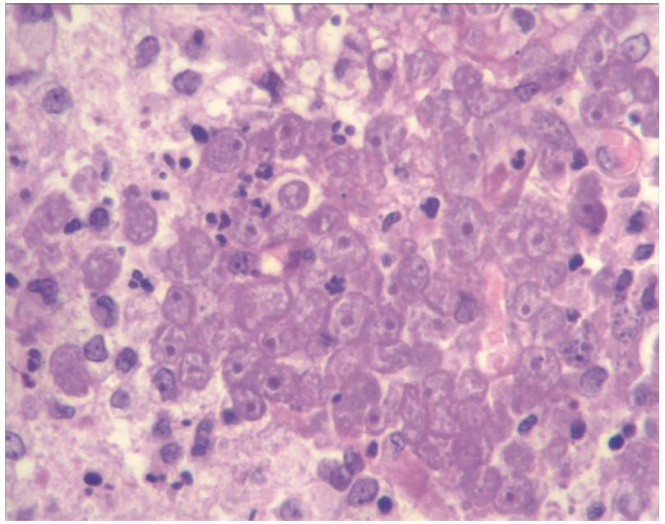


Fig. 5.15. Granulomatous amebic encephalitis. Trophozoites of *Balamuthia mandrillaris*. They have eosinophilic granular cytoplasm and a round nucleus.

GRANULOMATOUS AMEBIC ENCEPHALITIS

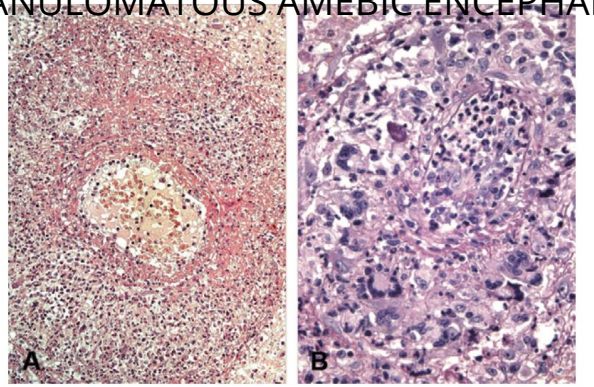


Fig. 5.14. Granulomatous amebic encephalitis. (**A**) Fibrinoid necrotizing panarteritis. (**B**) Incipient formation of perivascular granuloma.

Infections by free-living amoeba are highly fatal.

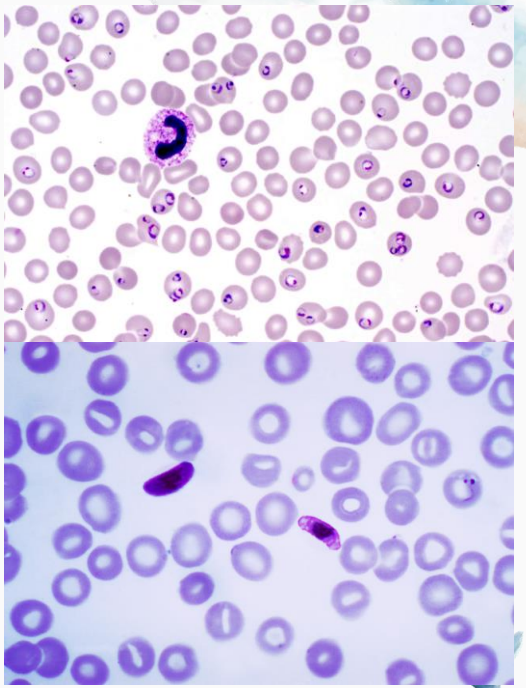
N. fowleri infections: Amphotericin B, rifampin, and fluconazole may be used.

A*canthamoeba* spp. and *B. mandrillaris* brain abscesses: surgery, pentamidine, and metronidazole are advised.

Handbook of Clinical Neurology, Vol. 114 (3rd series) Neuroparasitology and Tr

Cerebral malaria (*Plasmodium falciparum*)

- Annually, malaria causes more than 400,000 deaths in endemic regions, mostly in African children.
- it is usually considered a “tropical” disease, it is not restricted to the tropics, and approximately 10,000 cases are diagnosed every year in travelers.
- Although four species of Plasmodium can cause human malaria, only Plasmodium falciparum affects the CNS.



Cerebral malaria (*Plasmodium falciparum*)

- Bite of an infected Anopheles species
- Infective sporozoites reach the liver and infect hepatocytes
- In the hepatocytes, reproduce form a hepatic schizont, after which the cell breaks and releases merozoites.
- Merozoites infect red blood cells and alter their shape and function.
- In the red cell, now trophozoite stage reproduce again to form schizonts and rupture the erythrocyte, releasing a new generation of merozoites that infect new erythrocytes and continue the blood cycle.

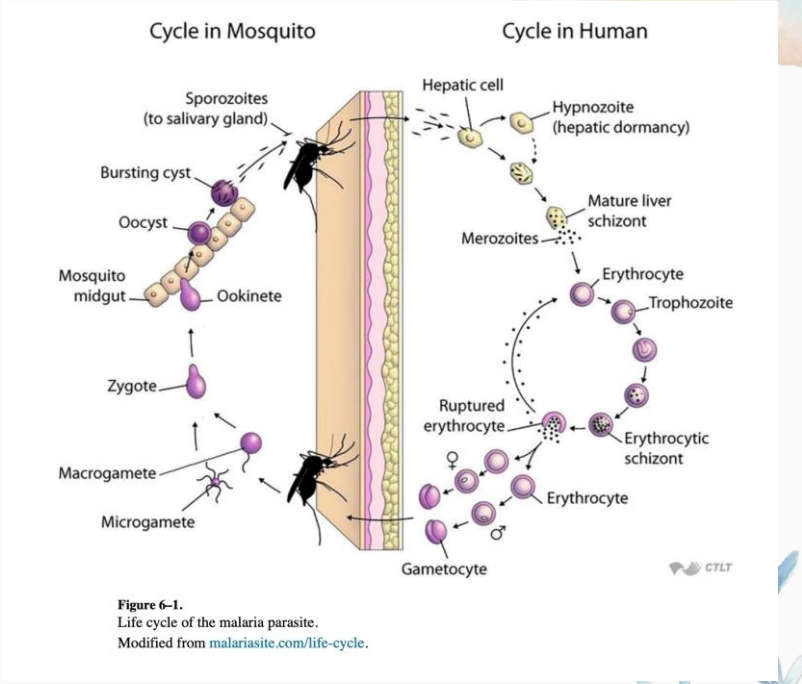
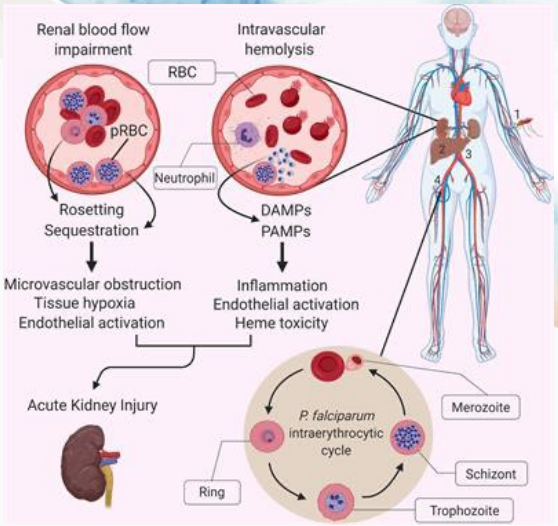


Figure 6–1.
Life cycle of the malaria parasite.
Modified from malariasite.com/life-cycle.

Cerebral malaria (*Plasmodium falciparum*)



Clinical Presentation

- Severe malaria
- Cerebral malaria
  - In children, cerebral malaria manifests as a febrile encephalopathy with seizures (in more than 70%); 6 months and 5 years
  - In adults, the progression to coma is gradual, seizures are less frequently observed (in 15% to 20%) and multiorgan system failure develops.
  - Untreated cerebral malaria is lethal in all cases
  - Mortality is high and some surviving patients sustain brain injury that manifest as long-term neurocognitive impairments.
  - Adult survivors generally have fewer neurologic complications but can rarely develop postmalaria neurologic syndrome, similar to acute disseminated encephalomyelitis (ADEM).

Cerebral malaria (*Plasmodium falciparum*)

Cerebral malaria

- Parasite never invades the brain tissues.
- Principal factor is the obstruction of blood vessels caused by parasitized red blood cell sequestration in small vessels of the brain, followed by microvascular congestion, reduced blood flow, hypoxia and glucose deprivation, blood–brain barrier breakdown, brain swelling, coma, and death.

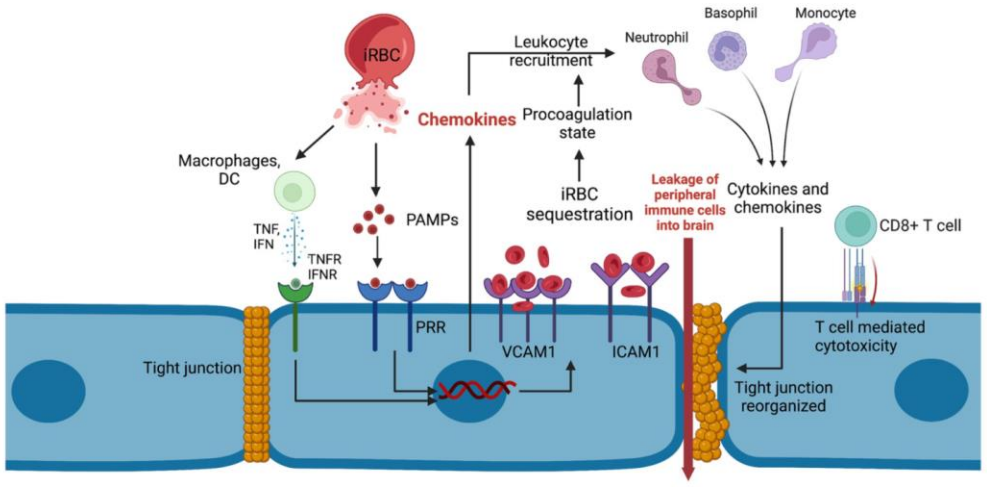


Fig 1. Pathogenic mechanisms leading to the breakdown of BBB. Rupture of iRBCs and release of merozoites into the bloodstream activate the macrophages and dendritic cells. This results in elevation of serum levels of TNF and IFN gamma. TNF and IFN gamma are known to up-regulate the expression of VCAM1 and ICAM1 on the endothelial cells. This in turn leads to an increase in the recruitment of iRBCs to the endothelial cells, thus promoting localised inflammation and procoagulation pathways. Meanwhile, the PRRs, such as Toll-like receptors expressed on the endothelial cells, recognise malarial PAMPs and trigger the secretion of proinflammatory cytokines like IL-6, IL-12, and TNF. The cytokines and chemokines released locally recruit leukocytes such as basophils, neutrophils, and natural killer cells to the site of inflammation. These cells, upon activation, release chemokines like MIP-1α and MIP-1β, which recruit more leukocytes to the site of inflammation. The elevated levels of chemokines and cytokines also induce reorganisation of tight junction proteins affecting the BBB integrity. Endothelial cells also present the parasitic antigen via MHC Class I molecules to CD8+ T cells in the brain. This triggers the CD8+ T cell–mediated cell death of endothelial cells mediated by granzyme B. These molecular events in tandem disrupt the BBB integrity and contribute to CM pathogenesis. This figure was made using BioRender.

Cerebral malaria

(*Plasmodium falciparum*)

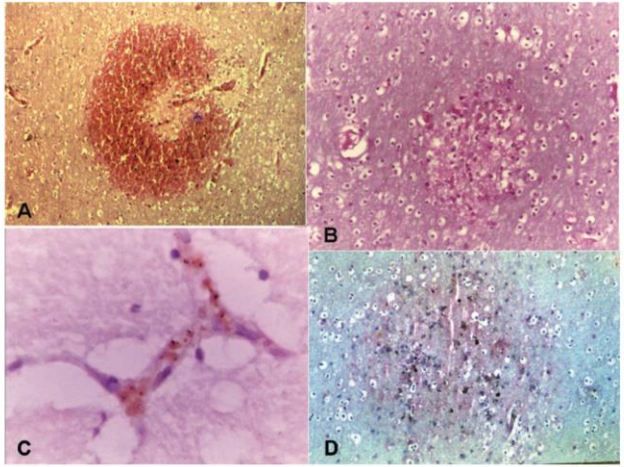


Fig. 5.2. Cerebral malaria. (**A**) Ring hemorrhage. (**B**) Dürck granuloma. (**C**) Postcapillary venule showing sequestration of parasitized red blood cells. Immunohistochemistry for *Plasmodium falciparum*. (**D**) Hemozoin pigment (malaria pigment) in the neuropil and within macrophages/microglia. (Courtesy of Professor M.I.S. Duarte, Department of Pathology, School of Medicine, University of São Paulo, São Paulo, Brazil.)

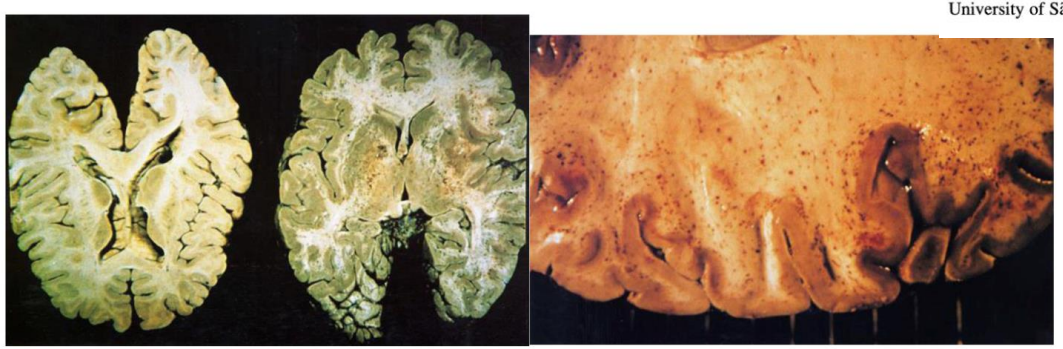


Figure 6–2. Pathology of cerebral malaria
A, Macroscopic pathology of cerebral malaria (*left*) compared to a normal brain (*right*) *B*, Close-up view of the brain demonstrating the typical "flea-bitten" appearance resulting from multiple ring hemorrhages in the white matter.

Handbook of Clinical Neurology, Vol. 114 (3rd series) Neuroparasitology and Tro
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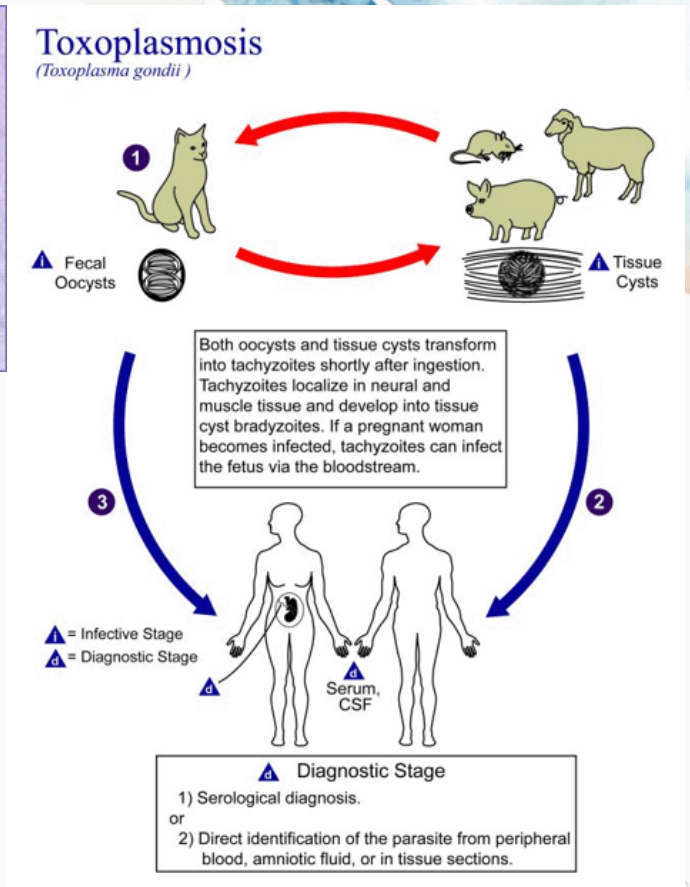
Continuum (Minneap Minn). 2021 August 01; 27(4): 943–962

Cerebral Toxoplasmosis (*Toxoplasma gondii*)



- The most common opportunistic infection of the CNS in AIDS due to reactivation of infection in the CNS.
- Acquired by eating undercooked meat or by accidental ingestion of contaminated cat feces.
- Zoonotic infections
- Immunocompetent hosts may also suffer from CNS toxoplasmosis during acute infections, and the brain of fetuses may be affected due to placental transmission of tachyzoites from women who acquire the disease during pregnancy.

Tunali, V.; Korkmaz, M. Emerging and Re-Emerging Parasitic Infections of the Central Nervous System (CNS) in Europe. *Infect. Dis. Rep.***2023**,*15*,679–699.

Cerebral Toxoplasmosis(*Toxoplasma gondii*)

Enter the CNS via 3 mechanisms

1. “Trojan horse” mechanism: infected immune cells exhibit increased motility and are capable of crossing endothelial barriers
2. Paracellular crossing mechanism
3. Transcellular crossing mechanism

Clinical presentation

- In Immunocompetent Patients
- In Immunocompromised Patients
- Toxoplasma gondii-Associated Diseases

Daher,D.;Shaghlil,A.; Sobh, E.; Hamie, M.; Hassan, M.E.; Moumneh, M.B.; Itani, S.; El Hajj, R.; Tawk, L.; El Sabban, M.; et al. Comprehensive Overview of *Toxoplasma gondii*-Induced and Associated Diseases. *Pathogens* **2021**, 10,1351.

Acute toxoplasmosis

- Develops after an incubation period of a few days following tachyzoites' spread and replication. It is asymptomatic in more than 80% of immunocompetent individuals.

- Flu-like symptoms including fever and mononucleosis-like symptoms, with cervical posterior adenopathy, myalgia.

- Occasionally, chorioretinitis

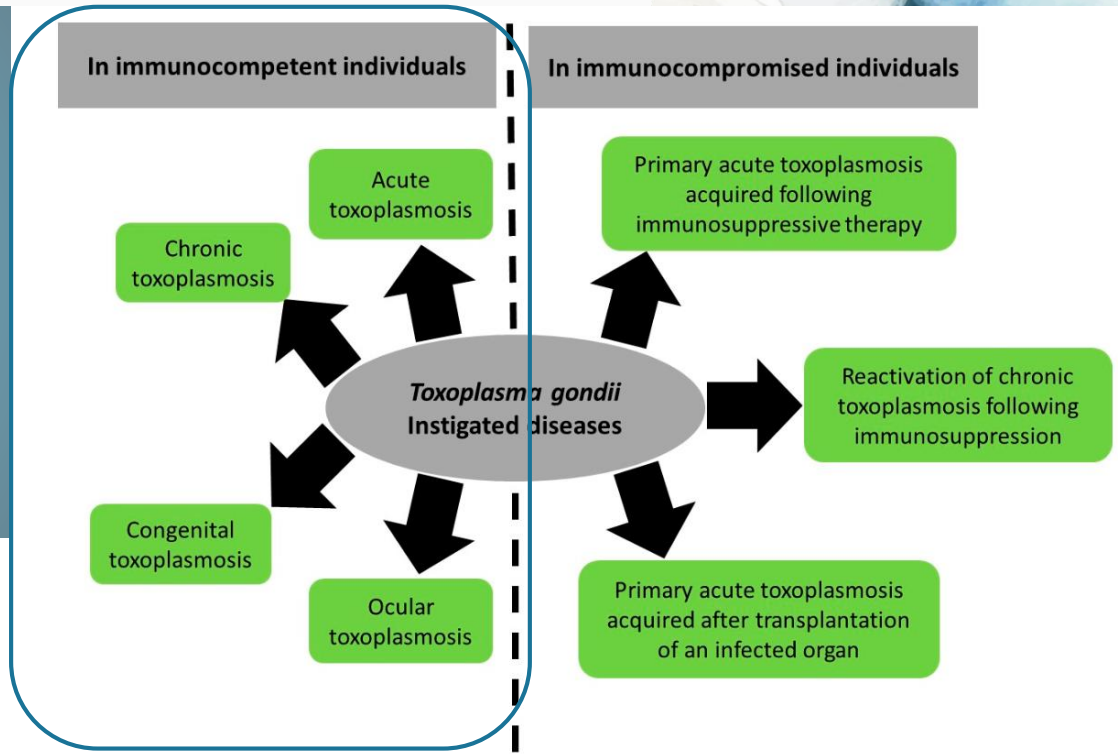


Figure 1. Summary of *Toxoplasma gondii*-induced diseases and their spectrum between immunocompetent and immunocompromised patients.

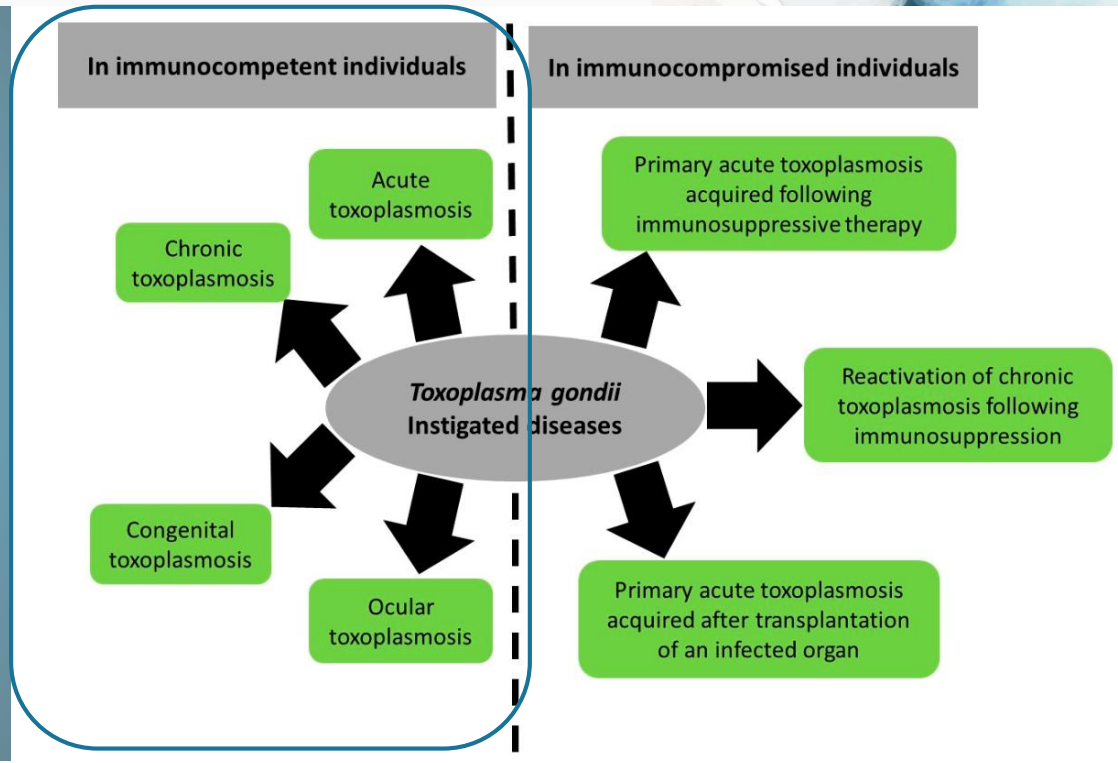
Daher,D.;Shaghlil,A.; Sobh, E.; Hamie, M.; Hassan, M.E.; Moumneh, M.B.; Itani, S.; El Hajj, R.; Tawk, L.; El Sabban, M.; et al. Comprehensive Overview of

Congenital toxoplasmosis

- In sero-negative pregnant women, primary infection occurs following the placental to the fetus

- 25% transmission takes place in the first trimester→ abortion, stillbirth, or a child born with severe abnormalities of the brain and eyes, such as hydrocephalus, intracranial calcifications, deafness, mental retardation, seizures, retinochoroiditis, and even blindness

- 54% - 65% occur in the second and third trimesters→ retinochoroiditis or learning difficulties after birth



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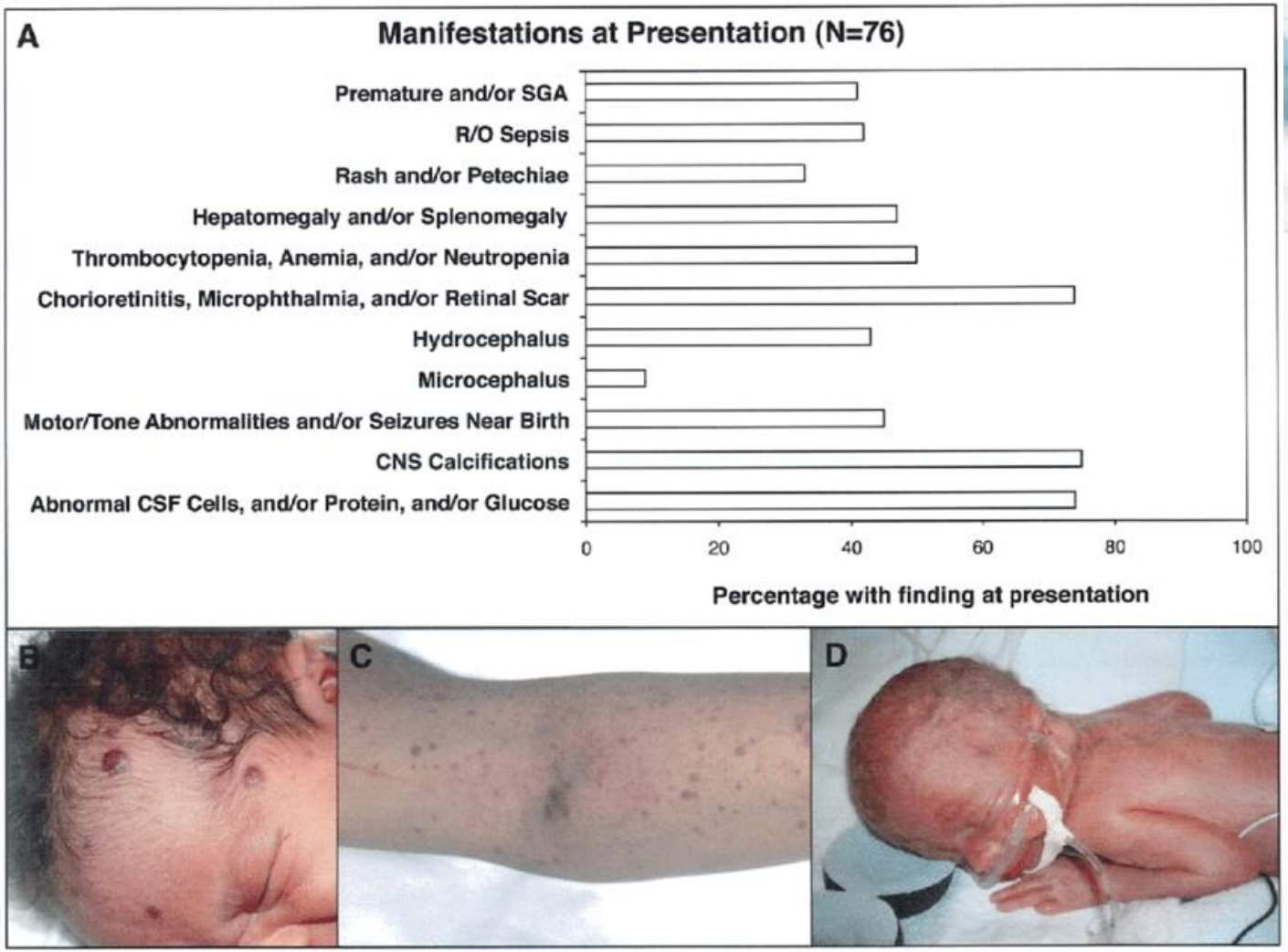
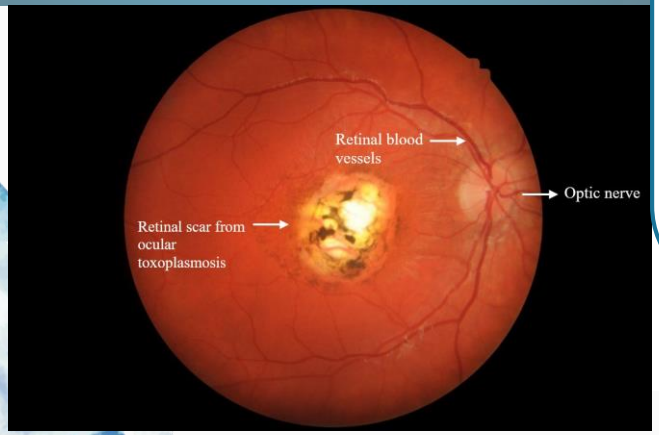
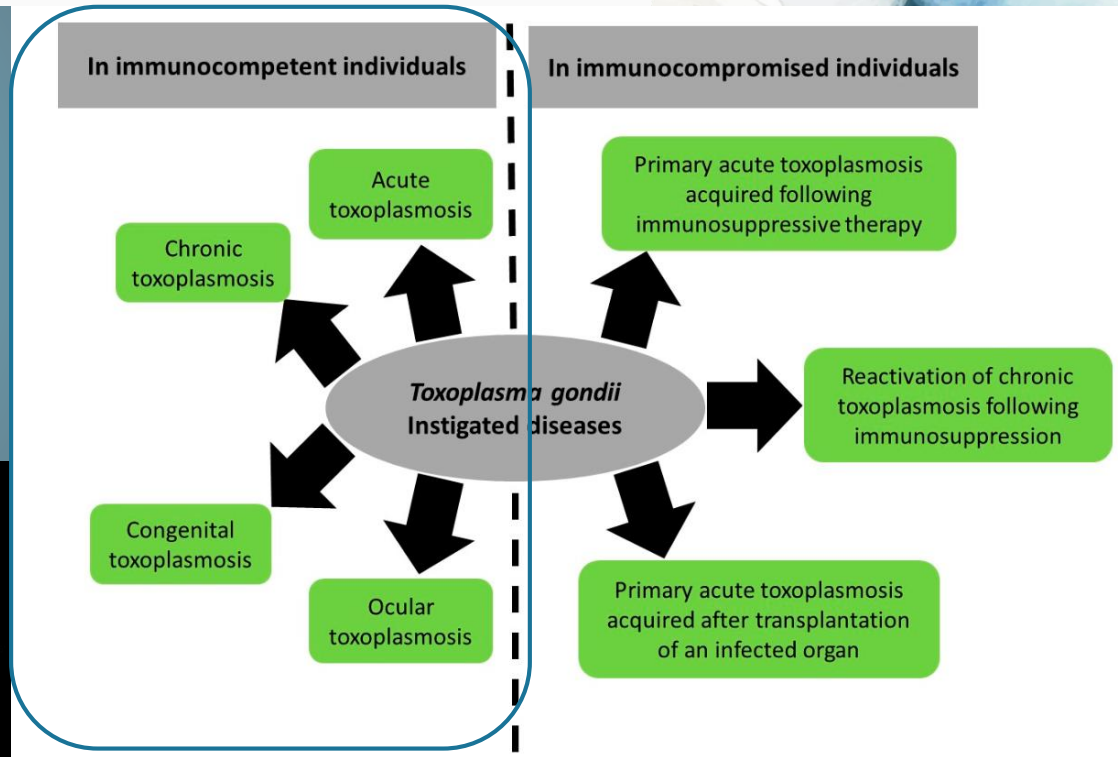

A
Manifestations at Presentation (N=76)
Premature and/or SGA
R/O Sepsis
Rash and/or Petechiae
Hepatomegaly and/or Splenomegaly
Thrombocytopenia, Anemia, and/or Neutropenia
Chorioretinitis, Microphthalmia, and/or Retinal Scar
Hydrocephalus
Microcephalus
Motor/Tone Abnormalities and/or Seizures Near Birth
CNS Calcifications
Abnormal CSF Cells, and/or Protein, and/or Glucose
0
20
40
60
80
100
Percentage with finding at presentation
B
C
D

Ocular toxoplasmosis

- Typically, retinochoroiditis is the most predominant indication of active intraocular inflammation. It presents with posterior uveitis, vitritis, focal necrotizing granulomatous retinitis, and reactive granulomatous choroiditis





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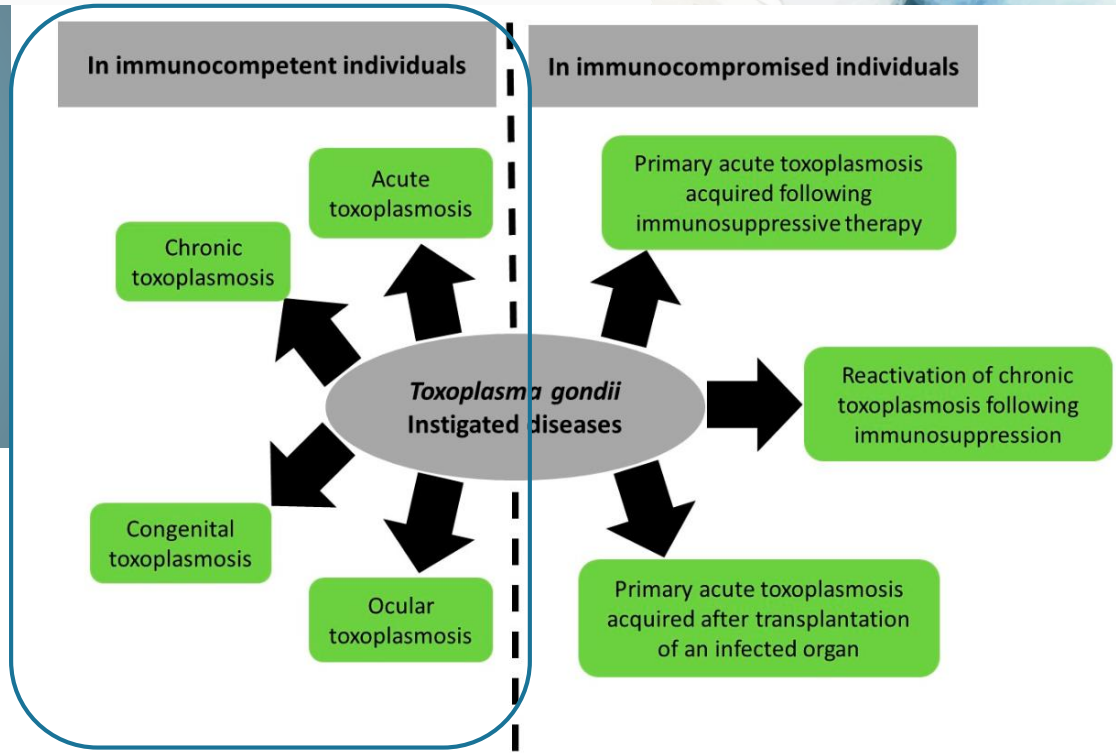
Chronic Toxoplasmosis

- Primarily neurotropic pathogen

T. gondii tachyzoites switch to forming bradyzoite cysts, which are the hallmark of the chronic phase of the infection.

- The immune response causes brain inflammation



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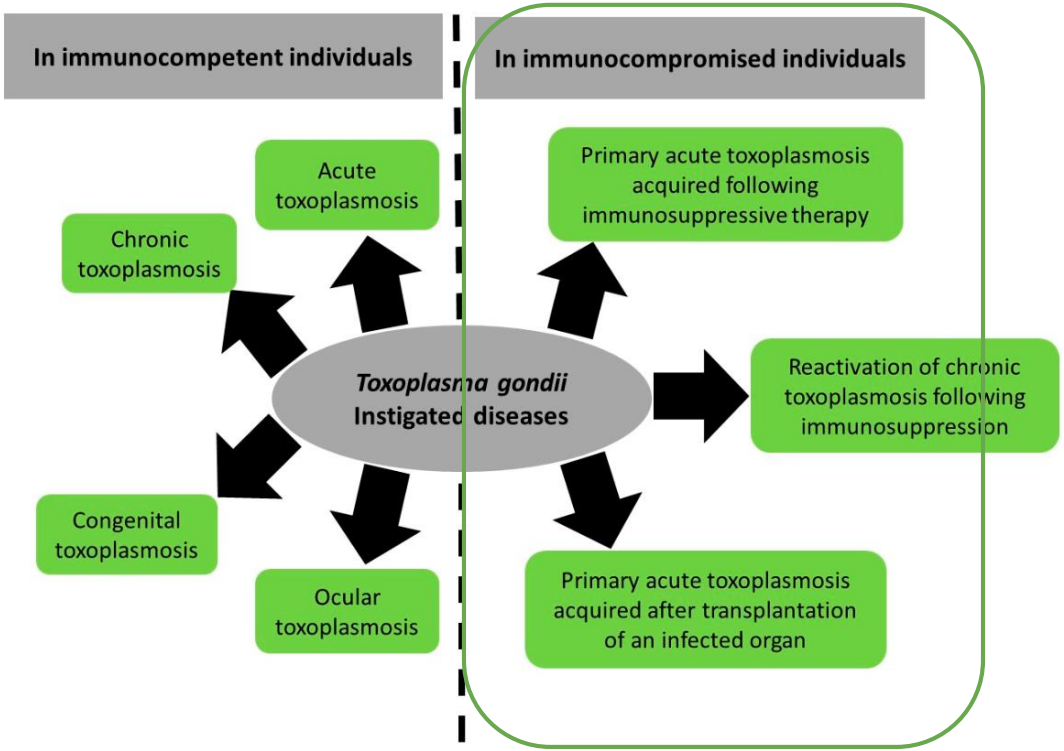

Figure 1. Summary of *Toxoplasma gondii*-induced diseases and their spectrum between immunocompetent and immunocompromised patients.

In HIV patients

- Toxoplasmic encephalitis is the predominant manifestation while pulmonary or disseminated toxoplasmosis is more characteristic of transplant patients.

- Most frequently diffuse encephalopathy, meningoencephalitis, cerebral mass lesions, headaches, confusion, poor coordination, and seizures.

- The reactivation of chronic toxoplasmosis CD4 count falls< 200 cells/mcl

Post transplant patients

- The highest risk of toxoplasmosis was described in orthotopic heart transplant recipients due to the propensity of bradyzoite cysts to form in striated muscles.

Daher,D.;Shaghlil,A.; Sobh, E.; Hamie, M.; Hassan, M.E.; Moumneh, M.B.; Itani, S.; El Hajj, R.; Tawk, L.; El Sabban, M.; et al.

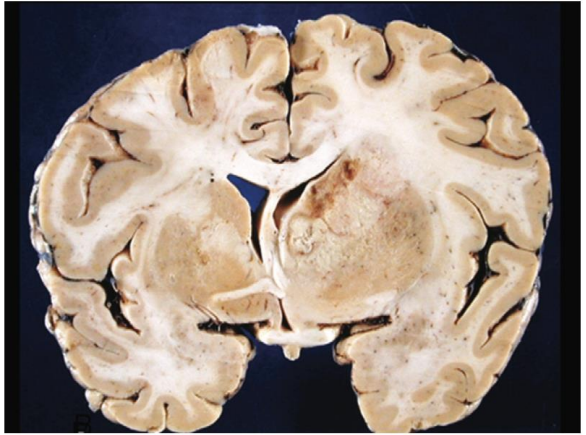

Fig. 5.10. Toxoplasmosis in human immunodeficiency virus infected patient. Mass lesion with necrosis in the basal ganglia.

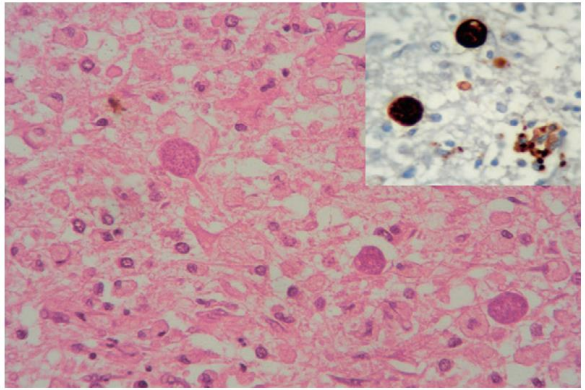

Fig. 5.11. Toxoplasmosis in human immunodeficiency virus infected patient. Periphery of necrotic focus showing macrophages and bradyzoites. Immunohistochemistry for *Toxoplasma gondii* shows bradyzoites and tachyzoites (inset).

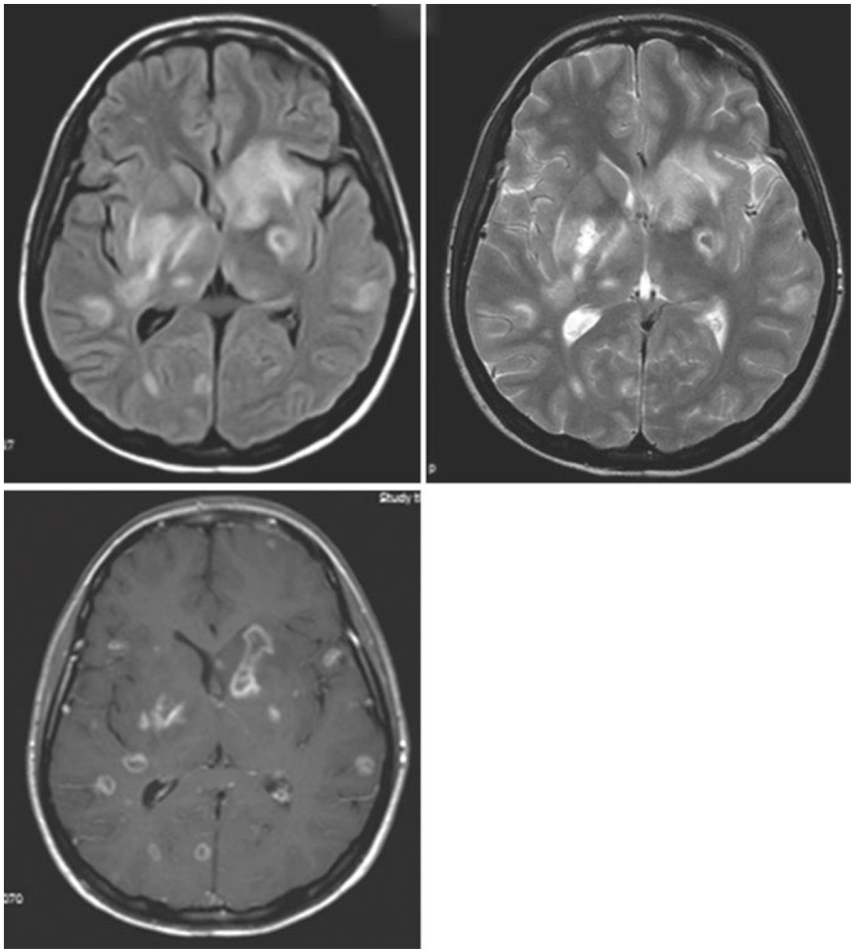

Fig. 9.1 FLAIR, T2-weighted, and contrast-enhanced T1-weighted MRIs of patient with AIDS and cerebral toxoplasmosis. Note multiplicity of lesions, predominance of involvement of the basal ganglia, and ring enhancement of most of them

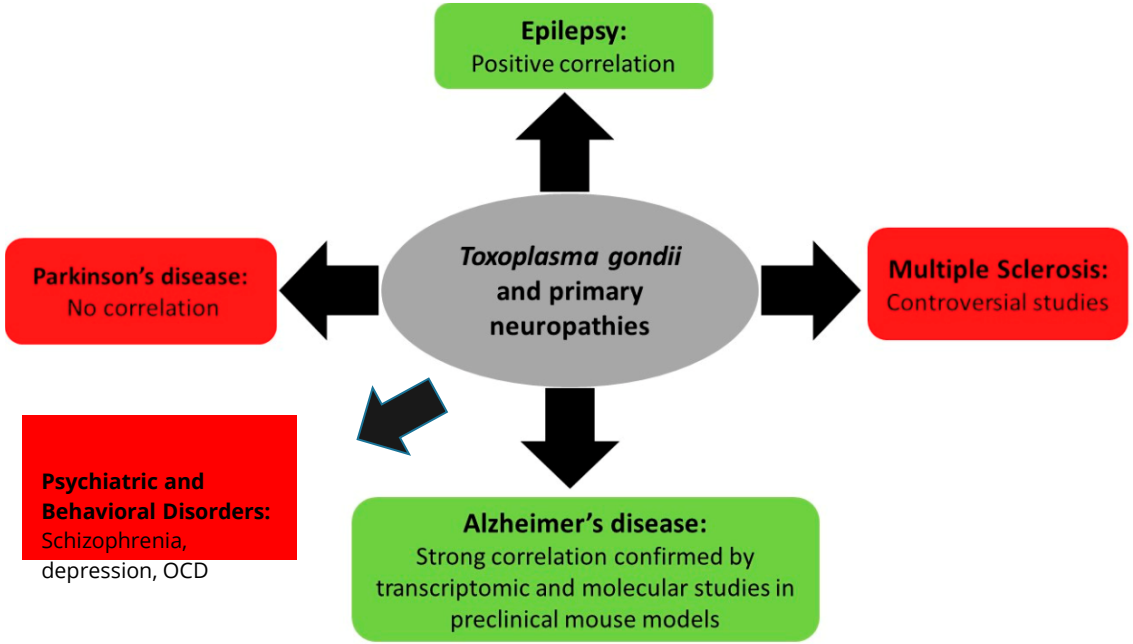

Figure 2. Summary of *Toxoplasma gondii*-associated primary neuropathy diseases and their outcome.

Daher,D.;Shaghlil,A.; Sobh, E.; Hamie, M.; Hassan, M.E.; Moumneh, M.B.; Itani, S.; El Hajj, R.; Tawk, L.; El Sabban, M.; et al.

Toxoplasmosis and Multiple Sclerosis

Associations between *T. gondii* and MS relied on data collected from five studies (up to April 2017, 669 MS patients and 770 controls).

Four out of five studies showed a negative association between *T. gondii* and MS and only one unveiled a positive association. Another study, which included 164 patients and 481 controls, revealed a negative.

Systematic review: random effects model for a global population of 752 MS cases and 1282 controls, added to the controversies. It reported a pooled odds ratio of 0.68 (95% CI = 0.50–0.93), suggesting that toxoplasmosis may play a protective role against MS.

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ean

REVIEW ARTICLE

***Toxoplasma gondii* and multiple sclerosis: A systematic review and meta-analysis**

Calogero Edoardo Cicero, Francesca Elsa Allibrio, Loretta Giuliano, Jaime Luna, Pierre-Marie Preux, Alessandra Nicoletti

First published: 09 August 2021 | https://doi.org/10.1111/ene.15055 | Citations: 5

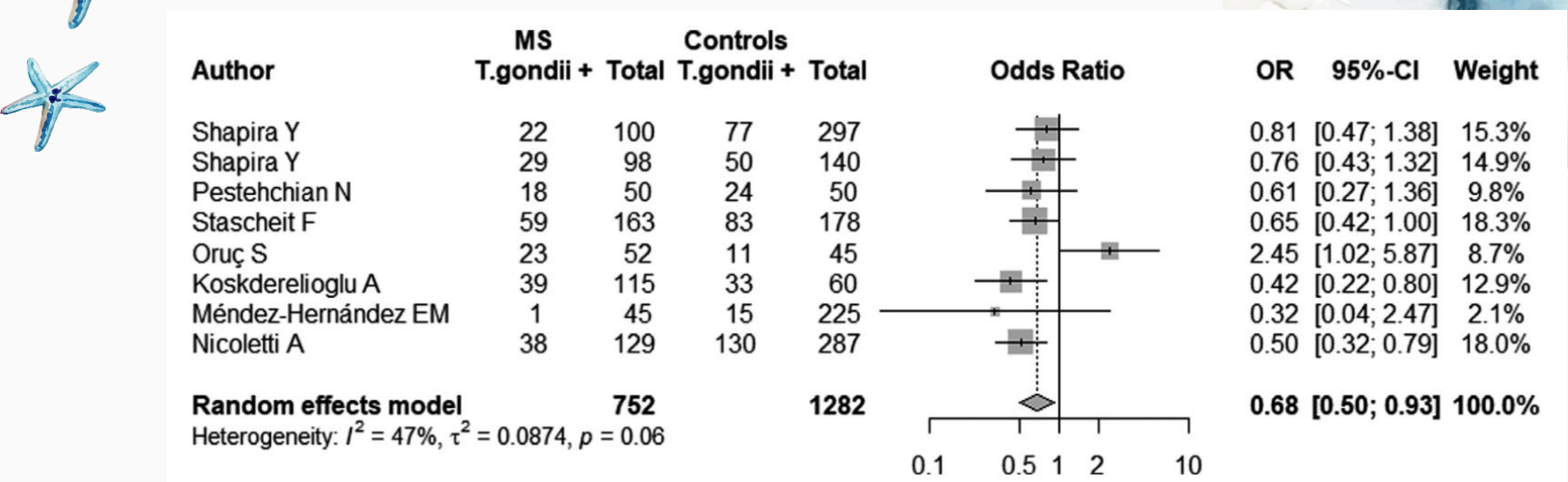

FIGURE 2 Forest plot of the association between *Toxoplasma gondii* seropositivity and multiple sclerosis (MS). CI, confidence interval; OR, odds ratio

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Toxoplasma gondii and multiple sclerosis: A systematic review and meta-analysis

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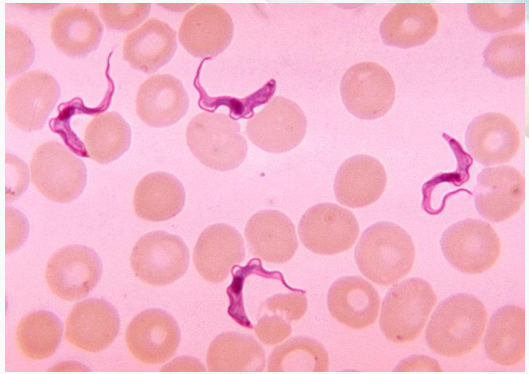
Cerebral Toxoplasmosis(*Toxoplasma gondii*)

Treatment and prophylaxis

- Recommended first-line therapy remains the synergistic combination of **pyrimethamine**, an inhibitor of dihydrofolate reductase (DHFR) enzyme, and **sulfadiazine**, an inhibitor of dihydropteroate synthase. This combination is usually administered with folinic acid (leucovorin) to reduce harmful side effects, amongst which is bone marrow suppression
- Absence of a gold standard treatment and a human vaccine against toxoplasmosis

Daher,D.;Shaghlil,A.; Sobh, E.; Hamie, M.; Hassan, M.E.; Moumneh, M.B.; Itani, S.; El Hajj, R.; Tawk, L.; El Sabban, M.; et al. Comprehensive Overview of *Toxoplasma gondii*-Induced and Associated Diseases. *Pathogens* **2021**, 10,1351

Trypanosomiasis



Vector-borne parasitic disease

Trypanosoma

Causes

Trypanosomiasis

West African Trypanosomiasis	East African Trypanosomiasis	American Trypanosomiasis
T.brucei gambiense	*T.brucei rhodesiense*	*T.cruzi*
Sleeping sickness		Chagas' disease
Transmitted by *Glossina* (tsetse fly)		Transmitted by *Triatoma* (winged bug)

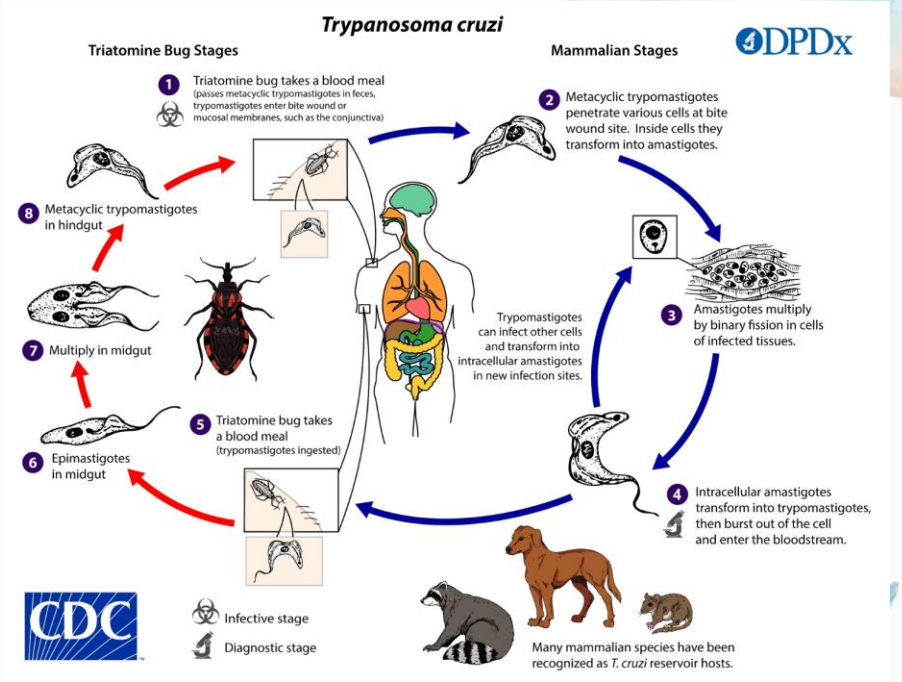
Dr. RAAFAT T. MOHAMED

Trypanosomiasis

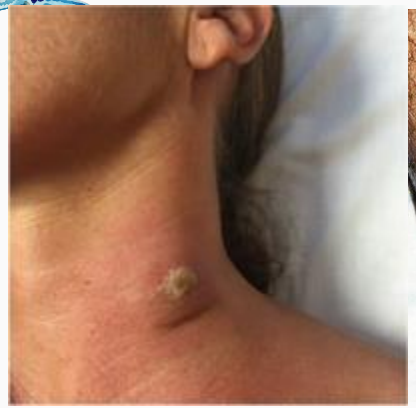
Trypanosoma cruzi

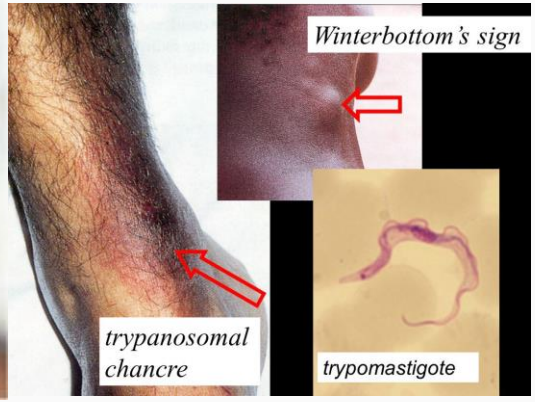
American trypanosomiasis (Chagas disease)

- Endemic to Latin America
- CNS involvement in CD may occur in a small percentage of patients in the acute phase.
- Reactivation of latent infection in chronic CD has been reported in immunosuppressed patients → Chagas meningoencephalitis
- The definitive diagnosis: parasite in CSF tests or by histologic analysis of the cerebral parenchyma.
- Nifurtimox and benznidazole may be used for patients during the acute phase of the disease
- Chronic Chagas' disease has no specific treatment.



Trypanosomiasis

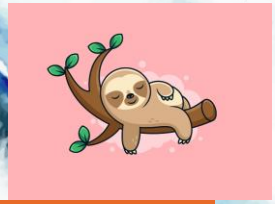




- CSF examination: moderate pleocytosis and the typical Mott cells.

Treatment

- West African trypanosomiasis, **pentamidine** is recommended for early phases and eflornithine for late stages.
- East African trypanosomiasis, **suramin** is the drug of choice for early stages and melarsoprol for late stages.



T. brucei gambiense, T. brucei rhodesiense

Human African trypanosomiasis (sleeping sickness)

- HAT infects the brain parenchyma by early seeding in the choroid plexus and secondary passage into the CSF, or by direct passage into the cerebral capillaries.
- Once these vessels are involved, allow the parasite to move into the brain tissue
- fever, cervical lymphadenopathy (Winterbottom's sign), and hepatosplenomegaly
- Stage 1, early hemolymphatic stage: parasite in blood and lymphatic tissue.
- Stage 2, late encephalitic stage: in the absence of treatment, the CNS becomes involved → meningitis to meningoencephalitis with brain edema and arachnoiditis.
- Terminal phase of the disease → death occurs without treatment

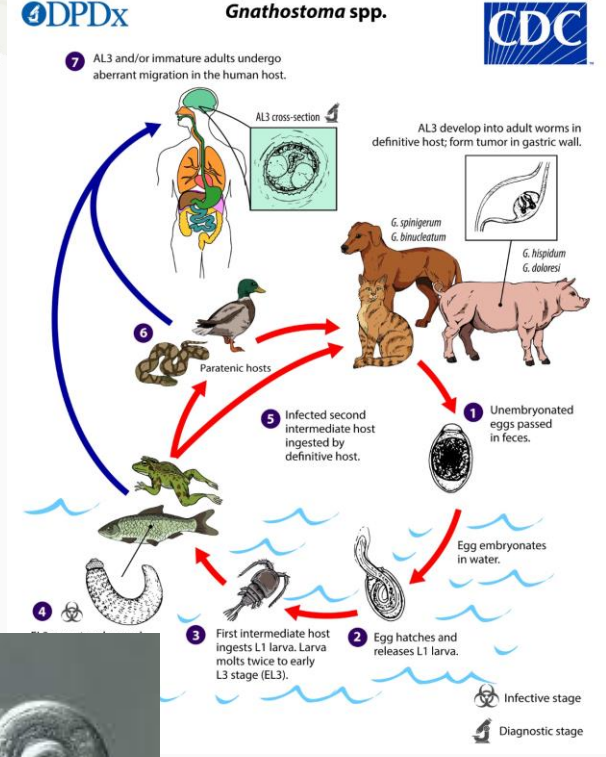
Table 1. Epidemiology, mode of transmission, diagnosis, and treatment of protozoal diseases of the CNS.

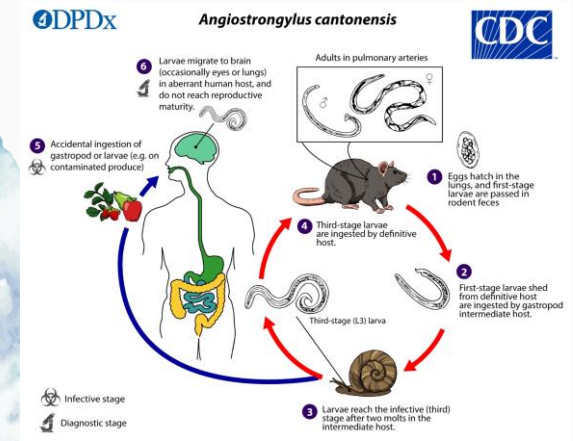
Parasites and Diseases	Countries with Reported Cases (Europe)	Mode of Transmission	Diagnosis	Treatment
Entamoeba histolytica Amebiasis	Turkey, Spain [13,14]	Ingestion of cysts	Radiology, serology, molecular	Metronidazole, surgical drainage
Free living amoeba *Naegleria fowleri* *Acanthamoeba* spp. *Balamuthia mandrillaris* *Sappinia*	Belgium, Czech Republic, Italy, the Netherlands, United Kingdom [20,22–24]	Trophozoites through nasal passage, olfactory nerve Cysts or trophozoites through eye, nasal passage, lung, or skin	Microscopy, molecular	Symptomatic
Plasmodium falciparum Cerebral malaria	United Kingdom, Switzerland [33,34], Italy, Germany, France, Denmark, Belgium [32]	Mosquito bite	Microscopy, molecular	Quinine and artemisinin
Toxoplasma gondii Toxoplasmosis	France, Spain, Czech Republic, United Kingdom, Germany, Denmark, Serbia [39]	Ingestion of oocysts or tissue cysts	Radiology, serology	Pyrimethamine and sulfadiazine
Trypanosoma brucei African trypanosomiasis (HAT)	France, Italy, Spain, the United Kingdom, Germany, the Netherlands, Belgium, Norway, Sweden, Switzerland, Poland [56]	Tsetse fly bite	Microscopy, molecular	Pentamidine, eflornithine, nifurtimox, melarsoprol, suramin
Trypanosoma cruzi South American trypanosomiasis (Chagas Disease (CD))	Spain, Portugal, Italy, France, the United Kingdom, Switzerland [54]	Metacyclic trypomastigotes through mucous membranes or skin abrasions	Microscopy, molecular	Nifurtimox, benznidazole

Table of contents

Eosinophilic meningitis

- Refer to the neurological complications related to infection with *Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, and *Baylisascaris procyonis*
- Humans become accidental hosts of these tissue nematodes after eating
  - raw snails (*A. cantonensis*),
  - undercooked fish or poultry (*G. spinigerum*),
  - raccoon feces (*B. procyonis*)





Eosinophilic meningitis

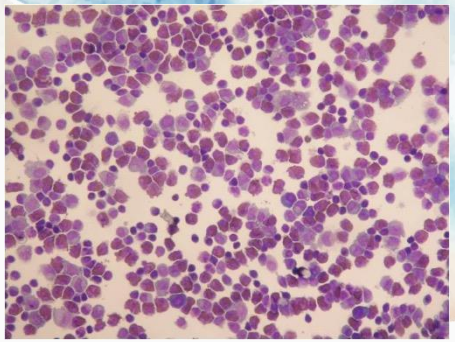
Angiostrongyliasis

Age (year) mean (range)	33 (15-70)
Sex, male	69%
Incubation, day	18 (1-90)
Signs or symptoms	
Headache	100%
Duration, day	7 (1-30)
Vomiting	47%
Stiff neck	54%
Fever (T >38.0OC)	7%
6th cranial nerve palsy	4%
7th cranial nerve palsy	2%
Hyperesthesia	7%

50% Normal neurological exam

A Case Report on Eosinophilic Meningitis Caused by *Angiostrongylus cantonensis*. Int J Med Sci. 2011

Angiostrongylus cantonensis



H&E stain for CSF

Ocular angiostrongyliasis

- Visual loss
- Found parasite at retina or vitreous
- +/- meningitis

ตารางที่ 3 การตรวจทางห้องปฏิบัติการ
ในผู้ป่วยเยื่อหุ้มสมองอักเสบชนิดอีโอสิโนฟิลิก

Blood eosinophilia (> 700 cells/mm3)	78%
CSF abnormalities	
High opening pressure (>300 mm H2O)	38%
WBC/mm3	711 (85-5,700)
Eosinophilia, %	45 (10-84)
Protein content, mg/dl	111 (27-574)
Glucose ratio, CSF/blood,	44 (17-100)

Something floating in Coconut juice
(Light reflection from eosinophil granule)
Angiostrongylus cantonensis

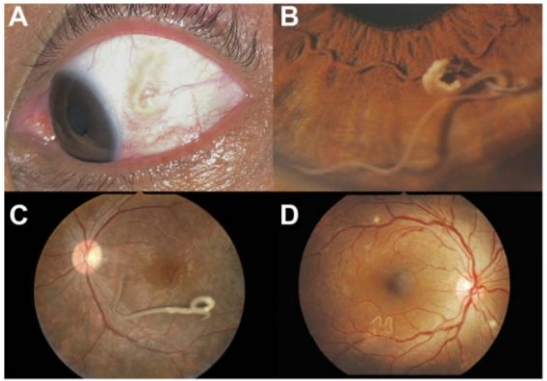


Figure 1 *Angiostrongylus cantonensis* larvae in subtenon space (**A**), aqeous humour (**B**), vitreous cavity (**C**), and subretinal space (**D**).

Sinawat S, et al. Ocular angiostrongyliasis in Thailand: a retrospective analysis over two decades. Clinical ophthalmology. 2019

Angiostrongylus cantonensis

Diagnostic test

Serology

ELISA/Western blot in blood

- Detect Specific Ab to 29kDa or 31kDa of Ag to parasite
- Only Available in KKU, MU
- Sensitivity 50-60%

PCR

- high specificity; rarely use

CT/MRI – non-specific

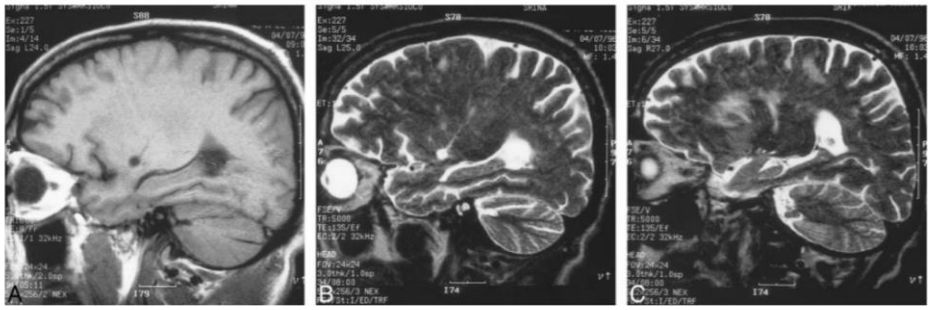


FIG 2. *A* and *B*, 45-year-old man. Sagittal T1-weighted (600/9/2) (*A*) and T2-weighted (5000/135/3) (*B*) MR images show a long track with a cavity in the left putamen (low signal in *A* and high signal in *B*).
C, Sagittal T2-weighted image (5000/135/3) shows abnormally high signal in periventricular, linear, and fuzzy nodular lesions.

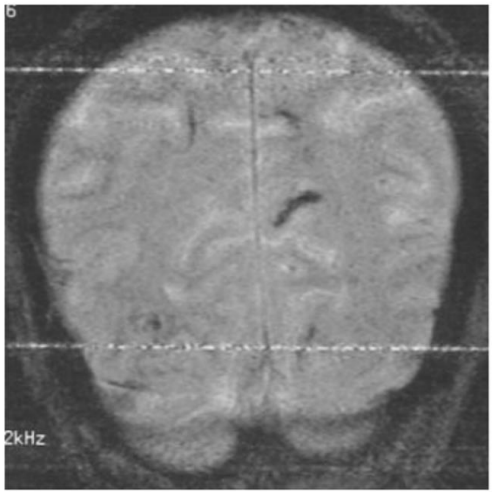
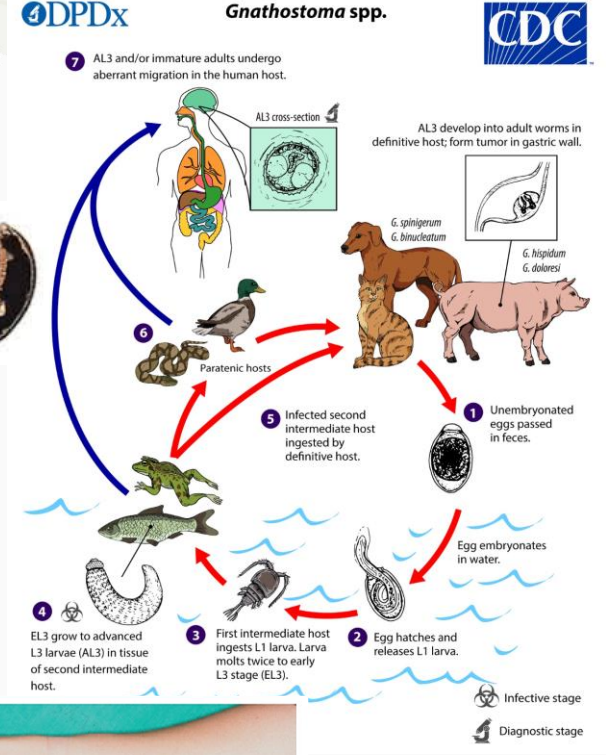


FIG 3. 64-year-old man. Coronal gradient-echo MR image (640/25/2) shows linear hypointense subcortical lesions, which might represent hemorrhagic tracks.

ysis in Eosinophilic Meningoencephalitis. SEA J Trop Med Public Health. 2001.

Gnathostoma spinigerum



Clinical presentation in CNS

- **Nerve root or Radicular pain***
  Electrical/shock-like pain at one limb
  Occurs 1-5 days
- **Myelopathy***
  Paraplegia/Quadriplegia
  Rare – Brown-Séquard or Cauda equina syndrome
- **Intracerebral hemorrhage (ICH)**
  Acute progressive headache + focal neurological deficit +/- SDH
- **Subarachnoid hemorrhage (SAH)**
  Sudden headache + meningism + AOC >> Coma, Seizure
- **Others – radiculomyelitis, radiculomyeloencephalitis**

Skin sign

- **Intermittent migratory swelling****
  Itching & Pain (Hallmark); migratory area
  Average 1-2 wk (range 2-3 d to 1 mo)
  Creeping eruption (rare)

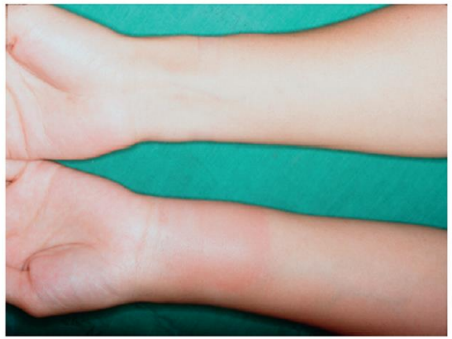
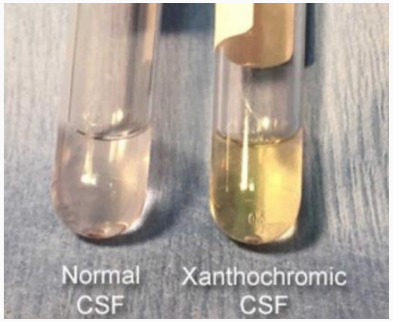


Fig. 15.6. Migratory swelling on left forearm caused by *G. spinigerum*.

Gnathostoma spinigerum



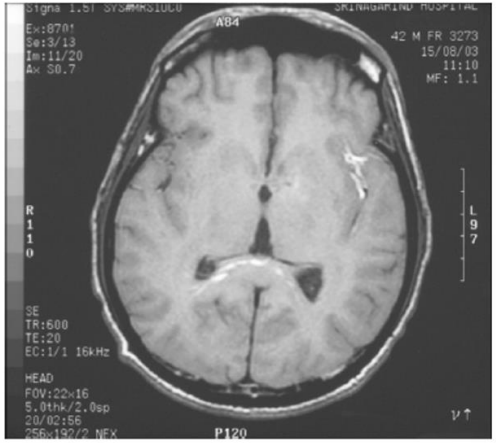


Fig. 15.8. MRI of the brain showed hemorrhagic tract at corpus collasum and subarachnoid hemorrhage at left sylvian fissure caused by *G. spinigerum*.

Diagnostic test

CBC: Eosinophilia *** (50% of cases)

LP – confirmed eosinophilic meningitis

- Pressure – normal, high
- **SAH – bloody CSF or Xanthochrome**
- WBC < 500 + Eosinophils
- Slightly elevation of protein
- Normal sugar

Serology

- ELISA/Western blot in blood
- Detect Specific Ab to 21kDa or 24kDa of Ag to parasite

CT/MRI brain

- Hemorrhagic tract lesion – migration of larvae
- Non-traumatic ICH, non-traumatic SDH, non-traumatic SAH

MRI spinal cord: Edema

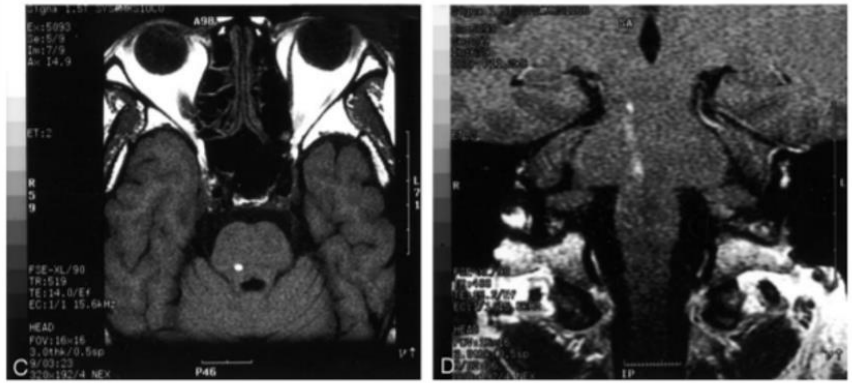


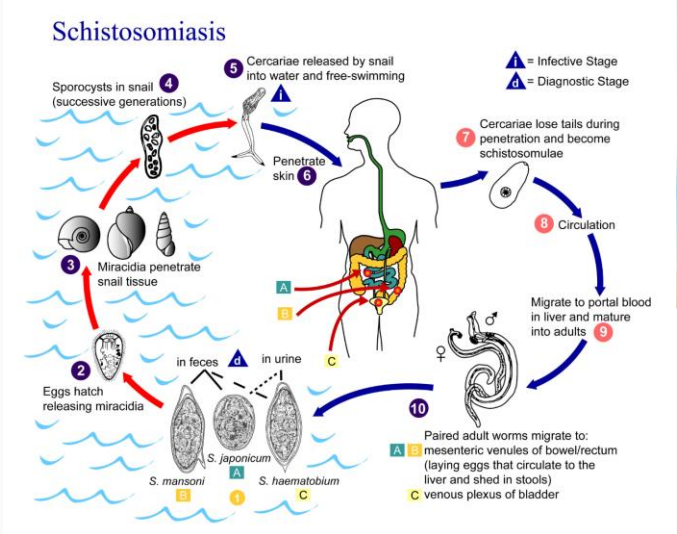
FIG 1. Case 1. MR images of spinal cord and brain.
A and *B*, Sagittal T2-weighted images, showing diffuse cord enlargement with abnormal high signal intensities.
C, Axial T1-weighted image, showing hemorrhagic spot at posterior midpons.
D, Coronal T1-weighted postgadolinium image, showing hemorrhagic tract at posterior midpons level.

Eosinophilic meningitis management

	Angiostrongylus cantonensis	*Gnathostoma spinigerum*
Specific treatment	- Albendazole 15 mg/kg/day divided in bid dose x 2 weeks NOT use albendazole alone! - Prednisolone 60 mg/day x 2 weeks For reduce inflammation	- CNS – Limited data, Depends on site (case by case) - prevent further migration before dying - Regimen – Albendazole 400 mg/day x 21 days OR Ivermectin 200 mcg/kg
Symptomatic treatment	Large volume LP releasing pressure 20-40 ml in case of high ICP	- Pain control – Headache, Root pain - Steroid – usually recommend in case of using antiparasitic agents

Schistosomiasis, *Schistosoma* spp. (*S. japonicum*, *S. mansoni*, *S. haematobium*)

- Endemic to sub-Saharan Africa, South America, the Caribbean, Southwest Asia, and the Middle East.
- Neuroschistosomiasis is a rare.

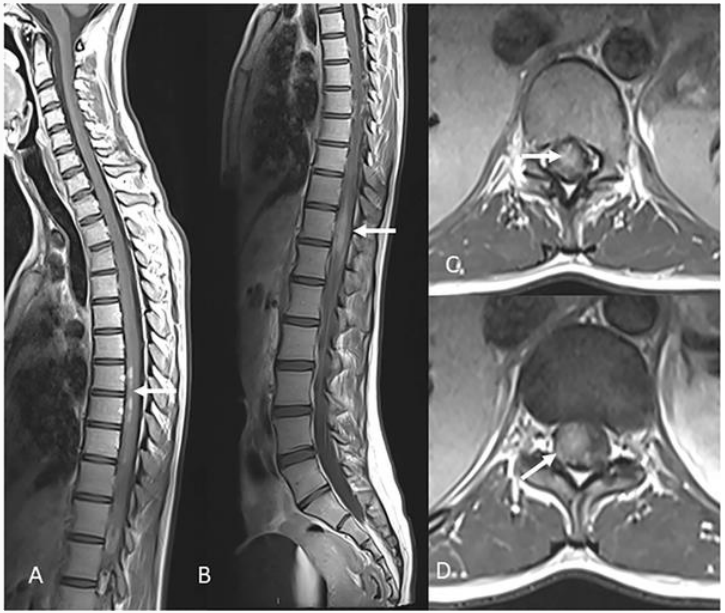


Clinical presentation

- The most common: headache
- Acute cerebral neuroschistosomiasis may produce a nonspecific encephalopathy that generally resolves within a few days or weeks.
- Chronic infection can present as a slowly expanding intracranial mass (pseudotumor), which can be a solitary mass or multiple mass lesions because of the development of parenchymal brain granulomas.
- Transverse myelitis is the most common presentation of spinal neuroschistosomiasis and is related to granulomatous lesions with inflammatory necrosis of the spinal cord.

Schistosomiasis, *Schistosoma* spp. (*S. japonicum*, *S. mansoni*, *S. haematobium*)

Lower spinal cord is most frequently affected, specifically at the levels of T11 through L1



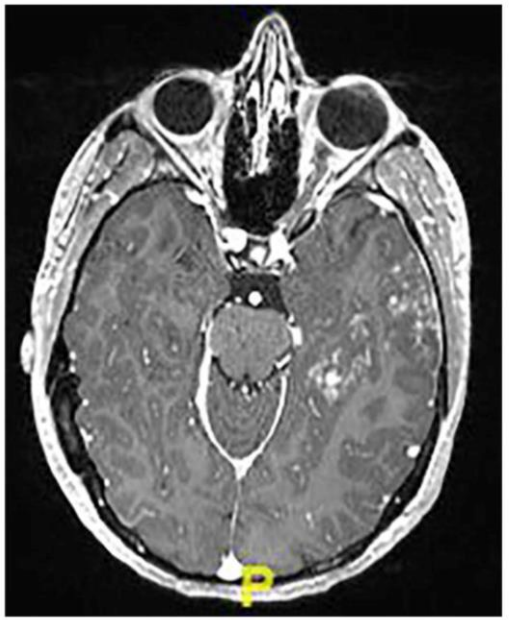
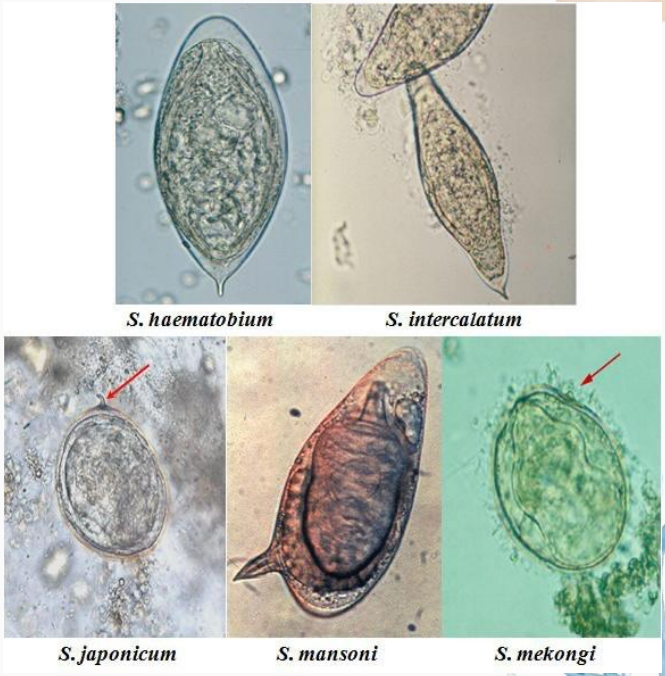


Figure 6–9.
Axial postcontrast T1-weighted MRI shows patchy enhancement in an arborized pattern in cerebral schistosomiasis. Reprinted with permission from Cho T, Continuum (Minneap Minn).[47] © 2018 American Academy of Neurology.

de Wilton A, Aggarwal D, Jäger HR, Manji H, Chiodini PL (2021) Delayed diagnosis of spinal cord schistosomiasis in a non-

Schistosomiasis, *Schistosoma* spp. (*S. japonicum*, *S. mansoni*, *S. haematobium*)

- Diagnosis requires the evidence of active Schistosoma infection.
- Direct visualization of eggs in stool or urine, punch biopsy from the rectal mucosa (higher sensitivity) or indirect assays measuring antibodies against schistosomal antigens have variable sensitivity depending on the timing and burden of infection.
- Serologic testing is not useful in individuals from endemic regions because schistosomiasis may cause asymptomatic infection and schistosomal antibodies may persist for years.



Cysticercosis (*Taenia solium*)

- Cysticercosis is the most common helminthic infection of the CNS.
- Neurocysticercosis represents a significant cause of morbidity and mortality, causing approximately 30% of cases of epilepsy in endemic regions, making it the most common preventable risk factor for adult acquired epilepsy.

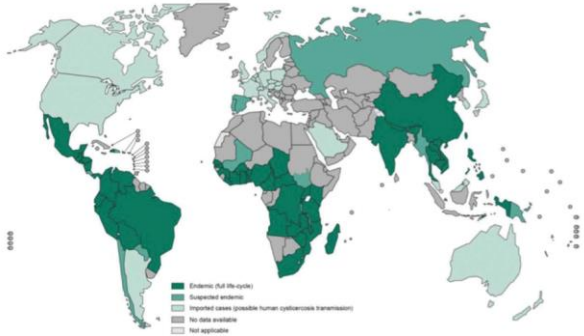
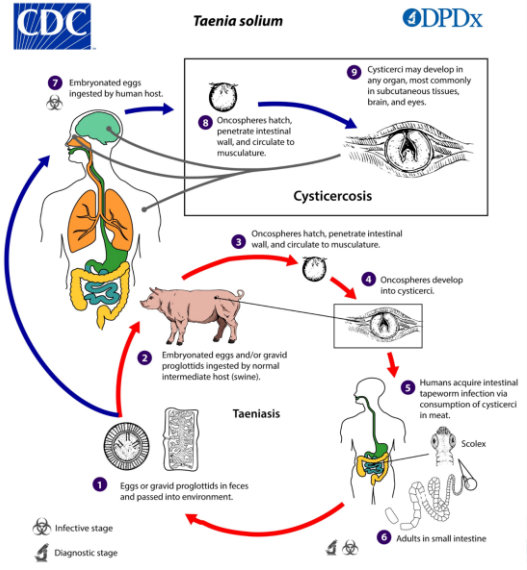


Figure 3. Countries and areas at risk for cysticercosis.
Reprinted from: World Health Organization. Assembling a Framework for Intensified Control of Taeniasis and Neurocysicercosis caused by Taenia solium, 2013. Available at: http://apps.who.int/iris/bitstream/1



Cysticercosis (*Taenia solium)*

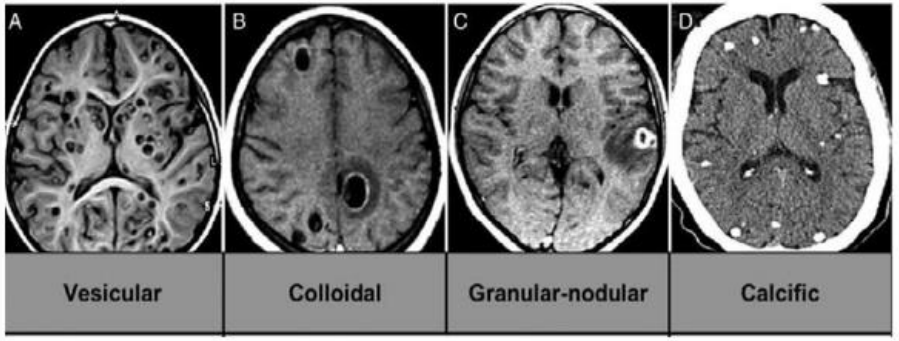


Figure 2: Vesicular 2. Colloidal 3. Granular-nodular 4. Calcific.

Clinical presentation

- Depending on the location, size, and number of lesions and host immune response
- Seizures and headaches are the most common symptoms and may occur in relation to parenchymal cysts in any stage.
- Extraparenchymal cysts in the cerebral ventricles or in the subarachnoid spaces (racemose cysts) can cause mass effect, hydrocephalus, intracranial hypertension, and chronic arachnoiditis
- Spinal cord cysticercosis occurs less commonly but may be an underrecognized.
- Chorea, dystonia, and myoclonus affected a younger population when compared to the general data.
- Patients particularly young women may present with hundreds or thousands of cysts with a diffuse inflammatory reaction and brain edema, a condition called cysticercotic encephalitis.

Continuum (Minneap Minn). 2021 August 01; 27(4): 943–962

Cysticercosis (*Taenia solium*)

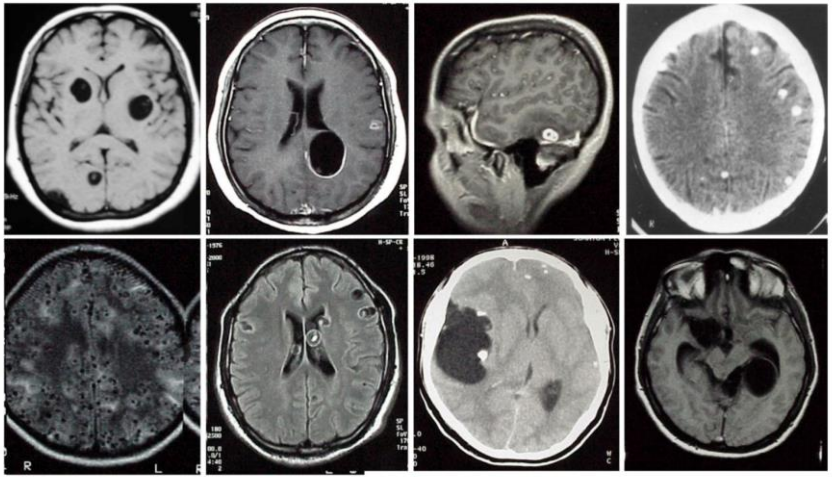


Figure 6–6.
Types and stages of neurocysticercosis. **Top: A. Multiple viable parenchymal cysts (axial MRI); B. Large occipital cyst with contrast enhancement (axial MRI); C. Enhancing lesion with contrast enhancement and edema (sagittal MRI), and D, Multiple parenchymal calcifications (non-contrasted CT). Bottom: E. Cysticercotic encephalitis (axial MRI); F. Cyst in the left lateral ventricle (axial MRI); G. Subarachnoid neurocysticercosis of the Sylvian fissure (axial MRI), and H. Subarachnoid neurocysticercosis in the basal cisterns (axial MRI).** Modified from García HH, et al, Current consensus guidelines for treatment of neurocysticercosis. Clin Microbiol Rev. 2002 Oct;15(4):747–56).

Recommend patients should be assessed with both CT and MRI.

Table 1: Revised diagnostic criteria for neurocysticercosis, only the neuroimaging part (Del Brutto *et al.*, 2017)

Neuroimaging criteria	Description
Major	Cystic lesions without a discernible scolex
	Enhancing lesions
	Multilobulated cystic lesions in the subarachnoid space
	Typical parenchymal brain calcifications
Confirmative	Resolution of cystic lesions after cysticidal drug therapy
	Spontaneous resolution of single, small enhancing lesions
	Migration of ventricular cysts documented on sequential neuroimages
Minor	Obstructive hydrocephalus
	Abnormal enhancement of basal leptomeninges

Continuum (Minneap Minn). 2021 August 01; 27(4): 943–962

Brain Circulation - Volume 6, Issue 4, October-December 2020

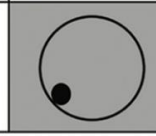
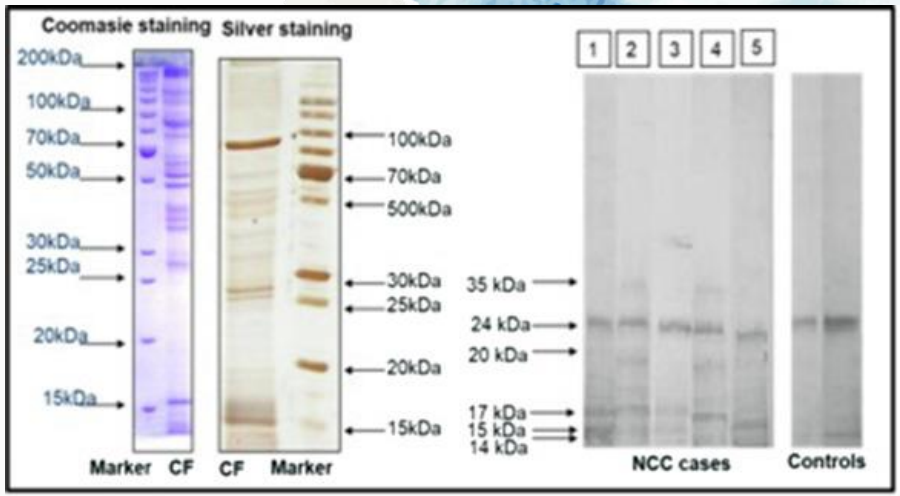
Stage	1. Non-Cystic	2.Vesicular	3.Colloidal-vesicular	4.Granular-nodular	5.Calcific
Description	Tissue invasion by the cysticercus	Viable parasite with intact membrane.	Parasite begins to degenerate. Cyst fluid becomes turbid. As the membrane becomes leaky edema surrounds the cyst. Host develops immune response. This is the most symptomatic stage.	Parasite degenerates. Host immune response decreases. Edema decreases as the cyst retract further.	Dead parasite. End-stage quiescent calcified cyst remnant; no edema.
Clinical manifestations	Usually asymptomatic	Seizure, intracranial hypertension, hydrocephalus, meningitis	Seizure		
Pathological mechanism	Inflammatory reaction	Compression and inflammatory reaction	Inflammatory reaction	Perilesional gliosis	Perilesional gliosis
Immunological response	Neutrophilic	Th 1 to Th 2	Th 1		Mixed Th 1 to Th 2
Radiological appearance (MRI features)	Local focus of edema. There might be nodular contrast enhancement. Usually no imaging studies are performed. Usually not correlated with imaging.	- "cyst with dot sign" represents the parasitic cyst with, usually eccentric, scolex. - Cyst (CSF-like signal): T1 hypointense, T2 hyperintense. - Scolex: isointense to parenchyma on T1 and T2, hypointense onT2 sequences, hyperintense on FLAIR - Usually no surrounding vasogenic edema	- Vasogenic edema surrounding the cyst. - Ring-like contrast enhancement - Formation of fluid-fluid level - Cyst: formation of capsule, hypointense on T2 sequences. Increased signal in the cyst fluid - scolex is seen early in the colloidal phase but gradually shrinks down and is harder to identify	- Residual cyst is smaller in size, thickening of the capsule. Isointense to the parenchyma on T1-/iso-hypointense on T2-weighted sequences - Calcified scolex (target appearance) - Minimal vasogenic edema might persist - Nodular or micronodular contrast-enhancement	- Calcified nodule without contrast-enhancement - Hypointense nodule on T2 sequences
Resume	Edema?	- Cyst + scolex. - Non-enhancement	- Ring enhancement. - Edema	- Decreased enhancement and edema - Begins calcification	- Obvious calcification
Imaging	-				

Figure 3: Stages of *Taenia solium* cysts in neurocysticercosis. Noncystic, vesicular, colloidal (colloidal-vesicular), granular (granular-nodular), and calcific (nodular)

Cysticercosis (*Taenia solium*)



Diagnostic test

- When neuroimaging tests are not conclusive, specific serology plays a major role in confirming the diagnosis.
- Antibody detection is frequently used because of its higher sensitivity, whereas antigen detection provides information on the presence of living parasites.
- EITB assay using lentil-lectin purified glycoprotein parasitic antigens in serum is the assay of choice for antibody detection, with 98% sensitivity and specificity close to 100%. (single brain cyst, the sensitivity may be as low as 70%)
- No advantage is seen in using CSF for EITB antibody detection.

Cysticercosis (*Taenia solium*)

Treatment

- For a single parenchymal cyst, albendazole at 15 mg/kg/d for 7 to 15 days is the regimen of choice.
- Multiple viable cysts, the combination of albendazole plus praziquantel at 50 mg/kg/d for 10 days has demonstrated superior efficacy.
- Surgical management is limited to the placement of VP shunts in patients with hydrocephalus.
- Corticosteroids for anti-inflammation
    - Dexamethasone at doses of between 4.5 and 12 mg/day.
    - Prednisone at 1 mg/kg/day may replace dexamethasone when long-term steroid therapy is required.

Revised Diagnostic Criteria and Degrees of Diagnostic Certainty for Neurocysticercosis[a]

Diagnostic criteria

- Absolute criteria
    - Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion
    - Visualization of subretinal cysticercus
    - Conclusive demonstration of a scolex within a cystic lesion on neuroimaging studies
- Neuroimaging criteria
    - Major neuroimaging criteria
        - Cystic lesions without a discernible scolex
        - Enhancing lesions[b]
        - Multilobulated cystic lesions in the subarachnoid space
        - Typical parenchymal brain calcifications[b]
    - Confirmative neuroimaging criteria
        - Resolution of cystic lesions after cysticidal drug therapy
        - Spontaneous resolution of single small enhancing lesions[c]
        - Migration of ventricular cysts documented on sequential neuroimaging studies[b]
    - Minor neuroimaging criteria
        - Obstructive hydrocephalus (symmetric or asymmetric) or abnormal enhancement of basal leptomeninges
- Clinical/exposure criteria
    - Major clinical/exposure
        - Detection of specific anticysticercal antibodies or cysticercal antigens by well-standardized immunodiagnostic tests[b]
        - Cysticercosis outside the central nervous system[b]
        - Evidence of a household contact with *Taenia solium* infection.
    - Minor clinical/exposure
        - Clinical manifestations suggestive of neurocysticercosis[b]
        - Individuals coming from or living in an area where cysticercosis is endemic[b]

Degree of diagnostic certainty

- Definitive diagnosis
    - One absolute criterion
    - Two major neuroimaging criteria plus any clinical/exposure criteria
    - One major and one confirmative neuroimaging criterion plus any clinical/exposure criteria
    - One major neuroimaging criterion plus two clinical/exposure criteria (including at least one major clinical/exposure criterion), together with the exclusion of other pathologies producing similar neuroimaging findings
- Probable diagnosis
    - One major neuroimaging criterion plus any two clinical/exposure criteria
    - One minor neuroimaging criterion plus at least one major clinical/exposure criterion

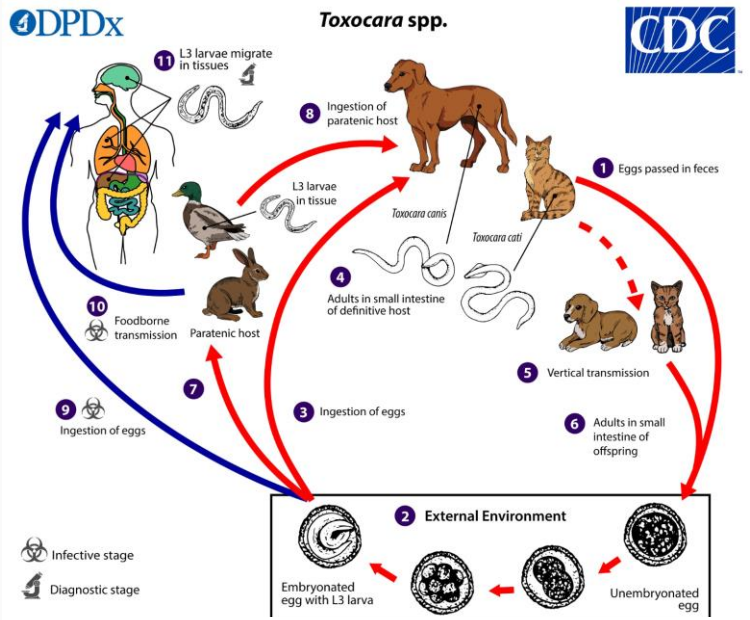
[a] Reprinted from Del Brutto OH, et al, J Neurol Sci.[38]

[b] Operational definitions. Cystic lesions: rounded, well defined lesions with liquid contents of signal similar to that of CSF on CT or MRI; enhancing lesions: single or multiple, ring- or nodular-enhancing lesions of 10 mm to 20 mm in diameter, with or without surrounding edema,

Toxocariasis (*Toxocara canis*, *T. cati*)

- OLM: affect the eye
- Mostly reported to occur in children between 3 and 16 years.
- Uni-ocular visual impairment might occur, accompanied by chronic endophthalmitis/retinitis and/or posterior/peripheral granulomata.

- NT: occur mainly in middle-aged people and less in children.
- One hundred cases of NT were identified in literature until April 2015.
- Predominant clinical pictures were myelitis (60%), encephalitis (47%) and/or meningitis (29%).



Visceral larva migrans (VLM)	Coughing, wheezing, pruritus, rash, lymphadenopathy, hepatosplenomegaly, nodules myocarditis, nephritis, eosinophilia present
Ocular larva migrans (OLM)	Chronic endophthalmitis, retinitis, posterior/peripheral granulomata, Uni-ocular visual impairment, blindness
Neurotoxocariasis (NT)	Fever, headache, meningitis, encephalitis, cerebral vasculitis, myelitis, epilepsy, neurodegenerative disease, cognitive and developmental delays
Covert toxocariasis (CT)	Nonspecific symptoms, asthma and developmental delays accompanied with eosinophilia and elevated IgE

Fig. 1. The range of clinical syndromes associated with human toxocariasis.

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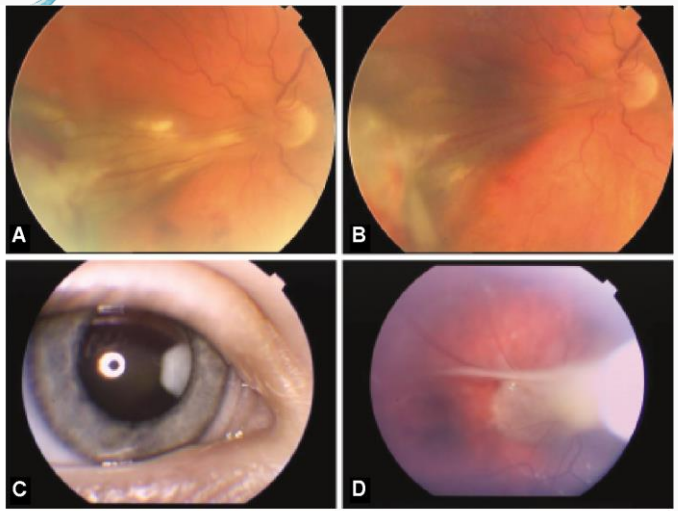
Case Report

Toxocariasis of the central nervous system: With report of two cases

Bouthouri Abir*, Mansour Malek, Mrissa Ridha

Department of Neurology, Military Hospital of Instruction of Tunis, Tunisia



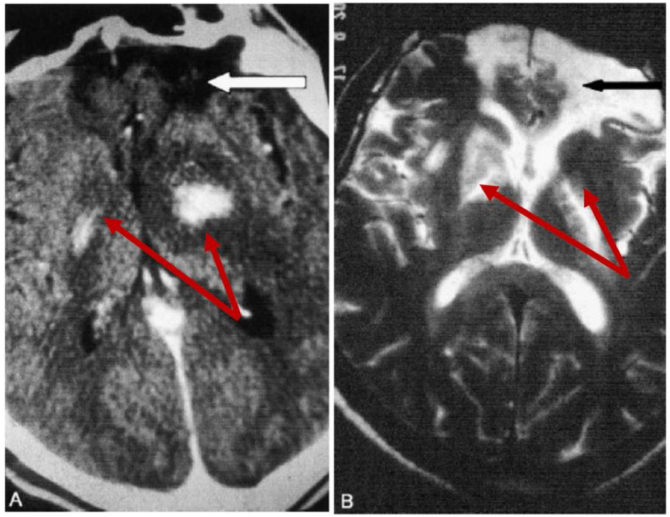


Fig. 1. (A) Brain CT scan showed bilateral hypodense capsulo-lenticular lesions with focal nodular contrast enhancement (red arrows). (B) Brain T2-weighted MRI: the lesions are hyperintense (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
NB: The frontal lesions are post-traumatic sequelae (white and black arrows).

NT result of hematogenous dissemination or mechanical damage caused by an immune-mediated inflammatory response.

Toxocariasis (*Toxocara canis, T. cati)*

Table 1
Key serological/immunological methods in current use for the detection of *Toxocara* infection(s) or exposure, and/or the diagnosis of toxocariasis, and brief description of purpose and performance.

Methodology	Purpose and performance	References
IgG-TCLA-ELISA	Detects specific total IgG in human serum; 92% sensitivity; 87% specificity	Jin et al. (2013)
IgG-TES-WB	Detects specific total IgG in human serum; "high" specificity; "minor" cross-activity	Magnaval et al. (1991)
IgG-TES-ELISA	Detects specific total IgG/IgG subclass in human serum; 60–98% sensitivity; 36–81% specificity	Noordin et al. (2005) Watthanakulpanich et al. (2008) Peixoto et al. (2011)
IgG-dTES-WB	Detects specific total IgG in human serum; no cross-reactivity with 32, 55 and 70 kDa fractions of dTES	Roldán et al. (2015)
IgG-dTES-ELISA	Detects specific total IgG in human serum; 100% sensitivity and specificity	Roldán et al. (2015)
IgG4-rTES-ELISA	Detects specific IgG4 subclass in human serum; 93% sensitivity and "increased" specificity	Mohamad et al. (2009)
IgG-DiM-BSA-ELISA	Detects specific total IgG in human serum; 92% sensitivity; 95% specificity	Elefant et al. (2016)

IgG: immunoglobulin G; TCLA: crude antigens from *T. canis* larvae; ELISA: enzyme-linked immunosorbent assay; TES: *Toxocara canis* excretory/secretory antigens; WB: Western blot; dTES: deglycosylated TES antigens; rTES: recombinant TES antigens; DiM-BSA: di-*O*-methylated coupled bovine serum albumin.

Table 2. Epidemiology, mode of transmission, diagnosis, and treatment of helminthic infections of the CNS.

Parasites and Diseases	Countries with Reported Cases (Europe)	Mode of Transmission	Diagnosis	Treatment
Angiostrongylus cantonensis Angiostrongyliasis	France, Germany, the Netherlands, Switzerland, Belgium, Croatia, Italy, Spain, United Kingdom [59,62]	Ingestion of raw or undercooked molluscs, crabs, or freshwater shrimp	Radiology	Symptomatic
Echinococcus granulosus Cystic echinococcosis *Echinococcus multilocularis* Alveolar echinococcosis	Greece, Italy, Turkey, Romania, Bulgaria [67] Belgium, Netherlands, Italy, Austria, Hungary, and Slovenia [68]	Ingestion of eggs	Radiology, serology	Surgery, PAIR, albendazole
Schistosoma spp.	France, United Kingdom, Spain, Portugal [79–83]	Skin penetration	Demonstration of eggs in stool or urine, serology	Praziquantel
Strongyloides stercoralis Strongyloidiasis	France, Belgium, Portugal [88–90]	Skin penetration	Demonstration larvae, serology	Ivermectin
Taenia solium Cycticercosis	Prevalent in both eastern and western Europe [97–99]	Ingestion of eggs	Radiology, serology	Surgery, albendazole, and praziquantel
Toxocara spp. Visceral larva migrans Ocular larva migrans Neurotoxocariasis	Spain, France, Denmark, Sweden [102,104,105]	Ingestion of eggs	Serology	Albendazole
Trichinella spp. Trichinellosis	France, Romania, Germany, Turkey, Serbia [110,114–117]	Ingestion of raw or undercooked pork	Demonstration larvae, serology	Symptomatic, albendazole

Overview treatment

Table 3. Currently available antiparasitic drug regimens for parasitic infections of the CNS.

Neurocysticercosis	• Albendazole with corticosteroids • Praziquantel (alternative to albendazole) with corticosteroids • Combined albendazole/praziquantel with corticosteroids if >2 active parenchymal cysts
Toxoplasmosis	• Sulfadiazine + pyrimethamine with leucovorin • Clindamycin (or atovaquone) + pyrimethamine with leucovorin (alternative) • Trimethoprim-sulfamethoxazole (alternative)
Echinococcosis	• Albendazole or mebendazole (alone or with surgery)
Schistosomiasis	• Praziquantel (after starting corticosteroid treatment)
Paragonimiasis	• Praziquantel • Triclabendazole
Cerebral malaria	Severe falciparum malaria • IV artesunate • IV quinine dihydrochloride or quinidine gluconate ◦ + doxycycline, tetracycline, or clindamycin
Toxocariasis	• Albendazole with corticosteroids • Mebendazole (alternative to albendazole) with corticosteroids
Onchocerciasis	• Ivermectin • Doxycycline
American trypanosomiasis	Acute or chronic infection • Benznidazole • Nifurtimox
African trypanosomiasis	Early infection • *Trypanosoma brucei gambiense* ◦ Pentamidine ◦ Suramin (alternative) • *Trypanosoma brucei rhodesiense* ◦ Suramin Late infection • *Trypanosoma brucei gambiense* ◦ Eflornithine + nifurtimox ◦ Eflornithine monotherapy ◦ Melarsoprol (alternative) with corticosteroids • *Trypanosoma brucei rhodesiense* • Melarsoprol
Angiostrongyliasis	• None (corticosteroids and symptomatic treatment only)

Prevention and control

In the year 2011, WHO adopted a roadmap for the control and elimination of NTDs, including many parasites that affect the CNS. Principles for action include:

(i) A focus on populations and interventions rather than specific diseases
(ii) The introduction of innovative tools for parasite detection and control
(iii) A multi-disease, intersectorial and interprogrammatic approach.

Community sensitization and mobilization campaigns

Chemoprevention

Intensified case- management

Symptomatic management

Vector control

Provision of safe food and water, sanitation and hygiene

Veterinary public health to prevent animal to human transmission.

Thank you