TOXOPLASMOSIS

DEFINITION

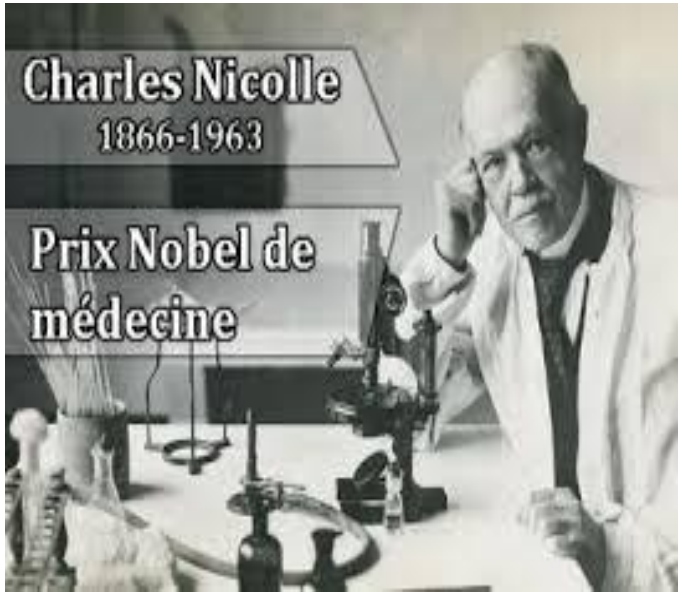
Toxoplasmosis is a protozoal invasion, with a predominantly latent or chronic course, characterized by a polymorphism of clinical manifestations -

damage to the nervous system, organs of the reticuloendothelial system, muscles, myocardium, eyes.

Infections with toxoplasmosis usually cause no obvious symptoms in adults. Occasionally, people may have a few weeks or months of mild, flu-like illness such as muscle aches and tender lymph nodes. In a small number of people, eye problems may develop. In those with a weak immune system, severe symptoms such as seizures and poor coordination may occur.
If infected during pregnancy, a condition known as congenital toxoplasmosis may affect the child.

History

Toxoplasma gondii **was first described in 1908 by Nicolle and in Tunisia, and independently by Splendore in Brazil. Splendore reported the protozoan in a rabbit, while Nicolle and Manceaux identified it in a North African rodent, the gundi (Ctenodactylus gundi). In 1909 Nicolle and Manceaux differentiated the protozoan from *Leishmania*. Nicolle and Manceaux then named it *Toxoplasma gondii* after the curved shape of its infectious stage (Greek root 'toxon'= bow).**

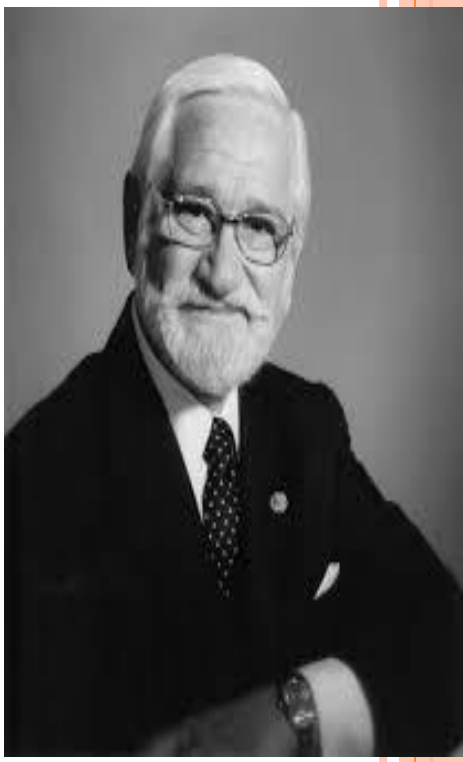


The first recorded case of congenital toxoplasmosis was in 1923, but it was not identified as caused by *T. gondii*. Histology revealed a number of "sporocytes", though Janků did not identify these as *T. gondii*.

It was not until 1937 that the first detailed scientific analysis of *T. gondii* took place using techniques previously developed for analyzing viruses. In 1937 Sabin and Olitsky analyzed *T. gondii* in laboratory monkeys and mice.

Sabin and Olitsky showed that *T. gondii* was an obligate intracellular parasite and that mice fed *T. gondii*-contaminated tissue also contracted the infection.

Thus Sabin and Olitsky demonstrated *T. gondii* as a pathogen transmissible between animals.



Albert B. Sabin

T. gondii **was first described as a human pathogen in 1939 at Babies Hospital in New York City.**
Wolf, Cowen and Paige identified *T. gondii* infection in an infant girl delivered full-term by Caesarean section. Wolf, Cowen and Paige isolated *T. gondii* from brain tissue lesions. Intracranial injection of brain and spinal cord samples into mice, rabbits and rats produced encephalitis in the animals.Wolf, Cowen and Page reviewed additional cases and concluded that *T. gondii* produced recognizable symptoms and could be transmitted from mother to child.
The first adult case of toxoplasmosis was reported in 1940 with no neurological signs.
In 1948, a serological dye test was created by Sabin and Feldman based on the ability of the patient's antibodies to alter staining of *Toxoplasma*.
The Sabin Feldman Dye Test is now the gold standard for identifying *Toxoplasma* infection.

Transmission of *Toxoplasma* by eating raw or undercooked meat was demonstrated by Desmonts et al. in 1965 Paris.
Desmonts observed that the therapeutic consumption of raw beef or horse meat in a tuberculosis hospital was associated with a 50% per year increase in *Toxoplasma* antibodies.
This means that more *T. gondii* was being transmitted through the raw meat.

In 1974, Desmonts and Couvreur showed that infection during the first two trimesters produces most harm to the fetus, that transmission depended on when mothers were infected during pregnancy, that mothers with antibodies before pregnancy did not transmit the infection to the fetus, and that spiramycin lowered the transmission to the fetus.

Toxoplasma **gained more attention in the 1970s with the rise of immune-suppressant treatment given after organ or bone marrow transplants and the AIDS epidemic of the 1980s.**
Patients with lowered immune system function are much more susceptible to disease.

Etiology

The causative agent –

coccidia Toxoplasma gondii –

an obligate intracellular parasite, is one of the simplest *(type Protozoa, class Sporozoa*).

It has the shape of a crescent, one end of which is pointed more than the other. In the center is a large core.
The length of the parasite is 4-7 microns.

Infective stages of the Parasite

The three infective stages of T. gondii include:

Tachyzoite: It is the rapidly dividing and invasive form and can invade any vertebrate cell type

Bradyzoite: These are the result of conversion from tachyzoites, they are slowly diving form and are present as tissue cysts, which can remain in the host throughout the lifetime in the muscles.

Sporozoite: It is the environmental form present in the oocysts

Mechanism of cell Invasion

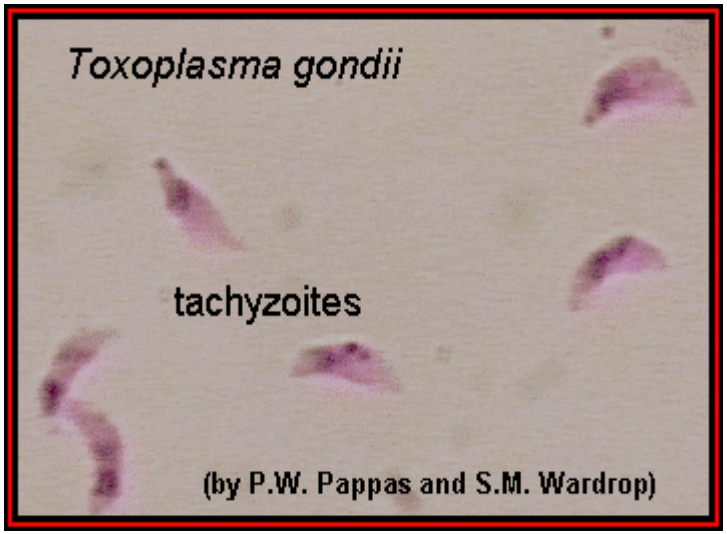
The initial step of invasion is attachment of the tachyzoite to the host cell membrane. A set of proteins help in the adherence and penetration of the host cell membrane, these proteins also enhance the growth and virulence of the parasite.

In the host cell the parasite forms a vacuole where it divides for 6 to 9 cycles after which the parasites are released into the circulation. It is an active process dependent on the increase in intracellular calcium stores.

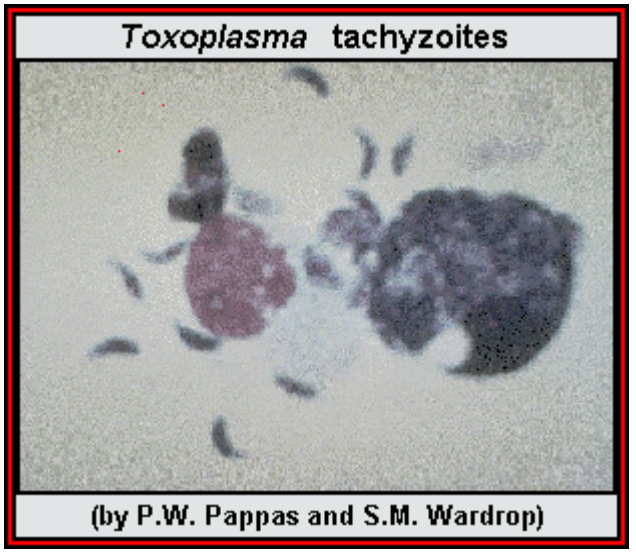
Microbiological characteristics

T. gondii **is a protozoan (eukaryote) which exists in several distinct stages.**

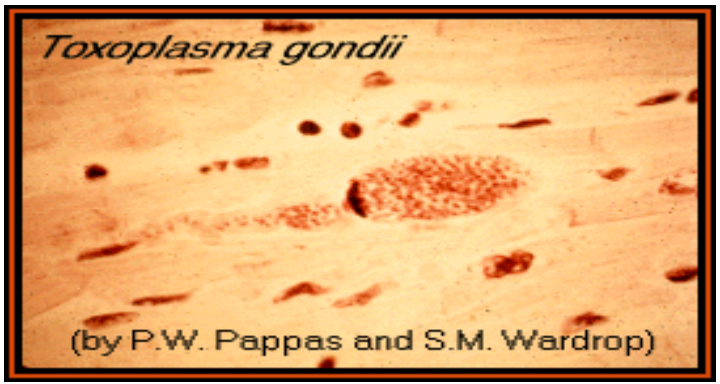
The tachyzoite stage:



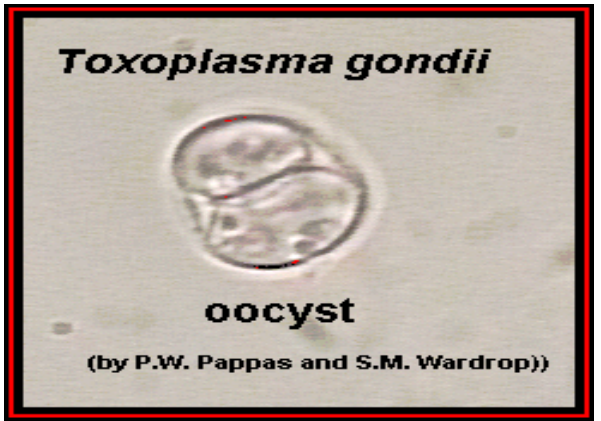
Tachyzoites rupturing host cell:



Bradyzoites in a Zoitocyst:



An Oocyst:



There are three major types of T. gondii responsible for the patterns of Toxoplasmosis throughout the world.
There are types I, II, and III.
These three types of *T. gondii* have differing effects on certain hosts, mainly mice and humans due to their variation in genotypes.

Type I: virulence in mice and humans, seen in people with AIDS.

Type II: non-virulent in mice, virulent in humans (mostly Europe and North America), seen in people with AIDS.

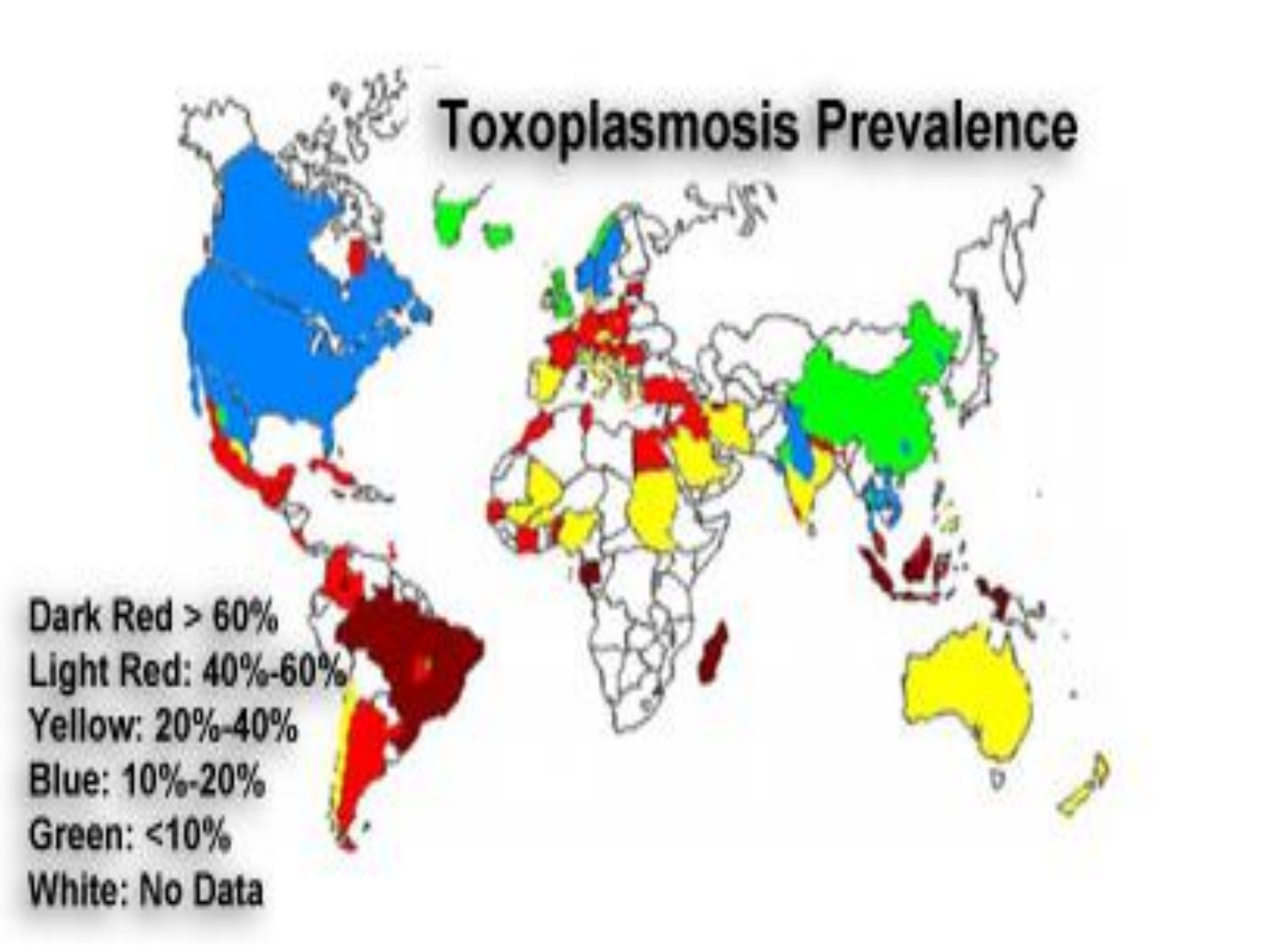
Type III: non-virulent in mice, virulent mainly in animals but seen to a lesser degree in humans as well.

Epidemiology

Toxoplasmosis is widespread, almost ubiquitous.
On the globe from 500 million to 1.5 billion people are infected with toxoplasmas.

For women of childbearing age, a survey of 99 studies within 44 countries found the areas of highest prevalence are within Latin America (about 50–80%),
parts of Eastern and Central Europe (about 20–60%),
the Middle East (about 30–50%),
parts of Southeast Asia (about 20–60%),
and parts of Africa (about 20–55%).

Toxoplasma gondii is considered the second leading cause of foodborne-related deaths and the fourth leading cause of foodborne-related hospitalizations in the United States.

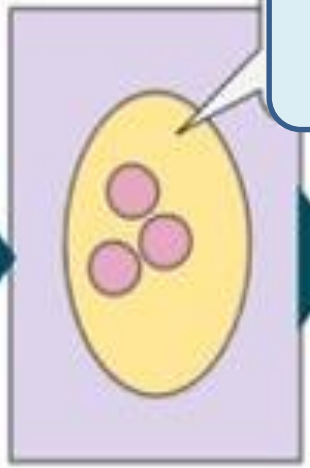

Toxoplasmosis Prevalence
Dark Red > 60%
Light Red: 40%-60%
Yellow: 20%-40%
Blue: 10%-20%
Green: <10%
White: No Data

The only known definitive hosts for *T.gondii* are members of family Felidae (domestic cats and their relatives).
The organism exhibits a definitive protozoan lifestyle. The life cycle begins with an oocyst in the intestines of cats.
The oocyst contains bradyzoites or sporozoites.
Oocysts enter prospective hosts through ingestion of cat fecal matter. Once inside a host, bradyzoites, after being released from the oocyst, infect the intestinal mucosa. Within the host cell, tachyzoites rapidly divide, eventually rupturing the cell. The released tachyzoites spread throughout the host, repeating the lysis process or forming zoitocysts (which are, like oocysts, filled with bradyzoites) in host tissue.
Three weeks after infection, there are no longer tachyzoites present in the tissues. The cysts reenter the cycle when ingested by another host, unless the host is a cat. In this case, oocysts will be formed in the cat's intestine and will be shed.

How is toxoplasmosis transmitted?

final host (the only one that spreads the parasite spores)

cat absorbs mouse oocytes or spores from the ground



oocysts contain toxoplasma spores

in the intestines of the cat's toxoplasma produce new spores that go out with feces

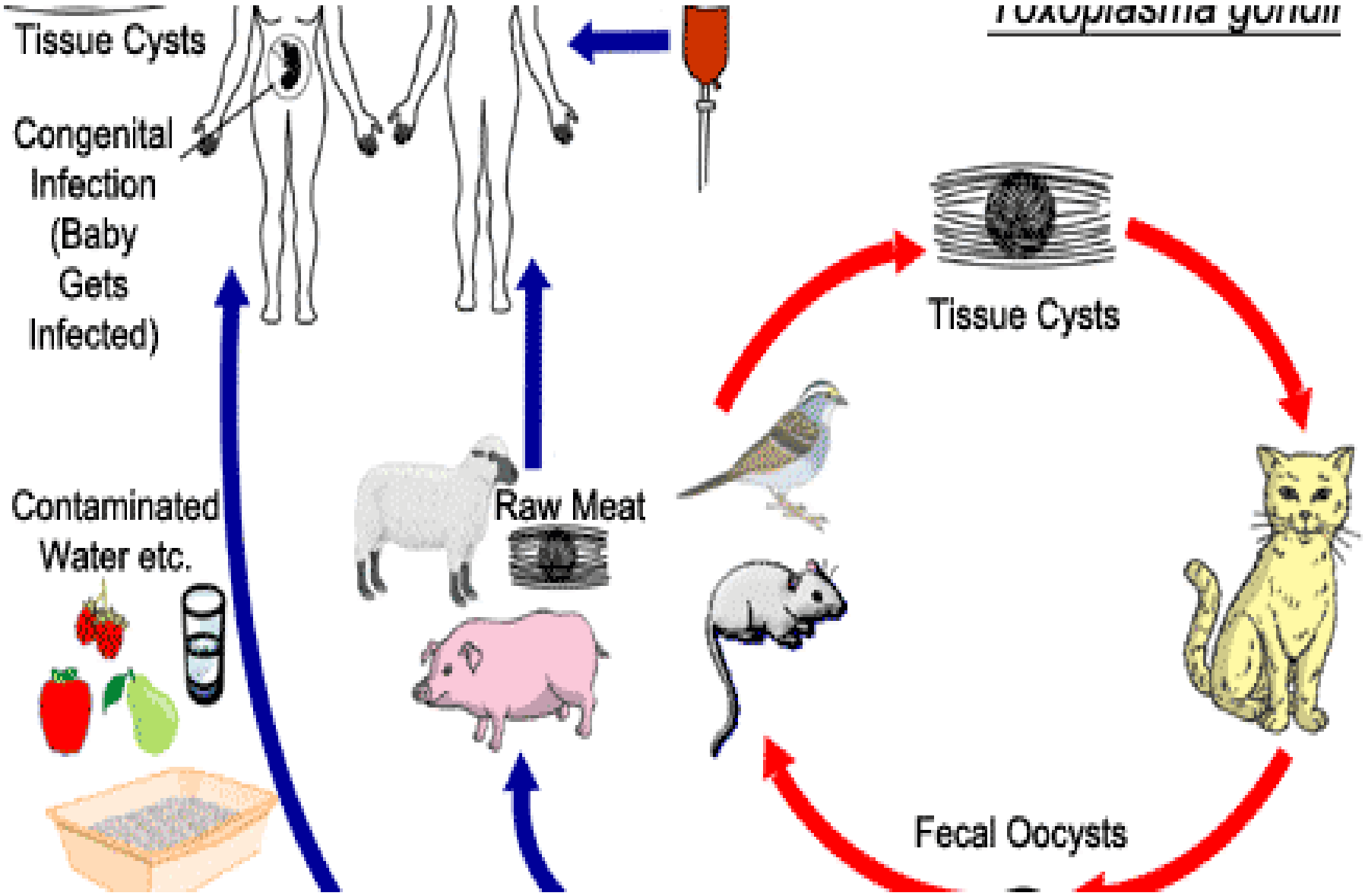
animals eat such feces

asexual spores are formed in the intestines of the intermediate host, which pass into the tissues of the body

excrement pollutes the ground and food

a person eats meat and vegetables that were in contact with land or animals and become infected with toxoplasmosis

Life Cycle Illustration



The unsporulated oocyst takes 1 to 5 days after excretion to sporulate (become infective). Although cats shed oocysts for only 1 to 2 weeks, large numbers may be shed.

Oocysts can survive in the environment for several months and are remarkably resistant to disinfectants, freezing, and drying, but are killed by heating to 70°C for 10 minutes.

Toxoplasmosis is not passed from person-to-person, except in instances of mother-to-child (congenital) transmission and blood transfusion or organ transplantation.

People typically become infected by three principal routes of transmission:

Foodborne

Animal-to-human (zoonotic)

Mother-to-child (congenital)

Rare instances

Transmission

Toxoplasmosis is generally transmitted through the mouth when *Toxoplasma gondii* oocysts or tissue cysts are accidentally eaten.

Congenital transmittance from mother to fetus can also occur.

Transmission may also occur during the solid organ transplant process or hematogenous stem cell transplants.

Oral transmission may occur through:

- **Ingestion of raw or partly cooked meat, especially pork, lamb, or venison containing *Toxoplasma* cysts: Infection prevalence in countries where undercooked meat is traditionally eaten has been related to this transmission method. Tissue cysts may also be ingested during hand-to-mouth contact after handling undercooked meat, or from using knives, utensils, or cutting boards contaminated by raw meat.**
- **Ingestion of unwashed fruit or vegetables that have been in contact with contaminated soil containing infected cat feces.**

Oral transmission may occur through:

- **Ingestion of cat feces containing oocysts: This can occur through hand-to-mouth contact following gardening, cleaning a cat's litter box, contact with children's sandpits; the parasite can survive in the environment for months.**
- **Ingestion of untreated, unfiltered water through direct consumption or utilization of water for food preparation.**
- **Ingestion of unpasteurized milk and milk products, particularly goat's milk.**
- **Ingestion of raw seafood.**

Transplacental infection

of the fetus can occur when the mother is infected during pregnancy.

It is necessary not to forget about two points:

1) with an infectious disease of the mother, the fetus may not be affected;

2)an infectious lesion of the fetus does not occur if the placenta is not infected.

The effect of invasion on the course of pregnancy and the condition of the fetus is realized by two mechanisms:

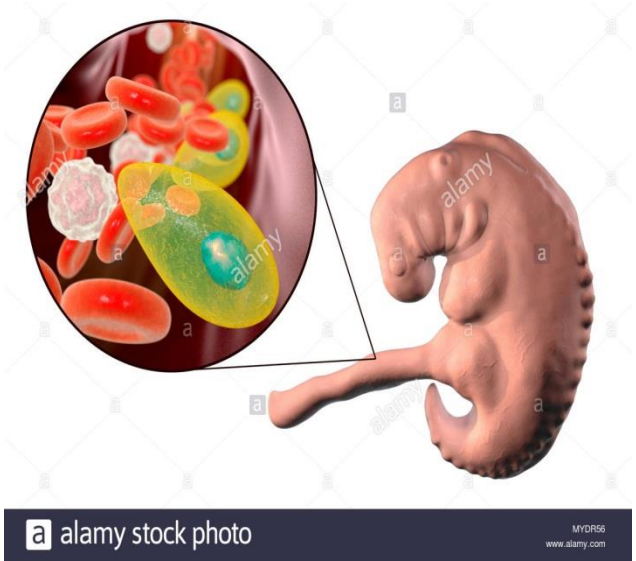
1) infection of the fetus, amniotic fluid, placenta and membranes, and a different degree of infection can be observed (generalized infection of the fetus and placenta, local infection of the fetus, teratogenic effects on the embryo and fetus, latent infection of the fetus with clinical manifestations in the postnatal period);

2) an indirect effect in the form of fever, disturbances in general homeostasis due to the severe course of infection, impaired fetoplacental barrier function, immune and hormonal imbalance.

When a mother is infected in the first trimester of pregnancy, congenital toxoplasmosis is observed in 15-20% and is severe.

When infected in the third trimester, 65% of newborns become infected.

If a woman is infected before pregnancy (for 6 months or more), intrauterine damage to the fetus does not occur, and if the infection occurred shortly before pregnancy, the risk of infection of the fetus is very small.

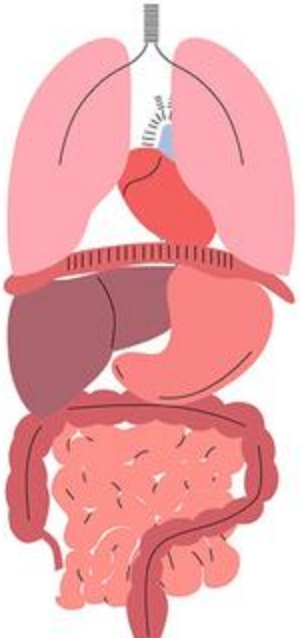


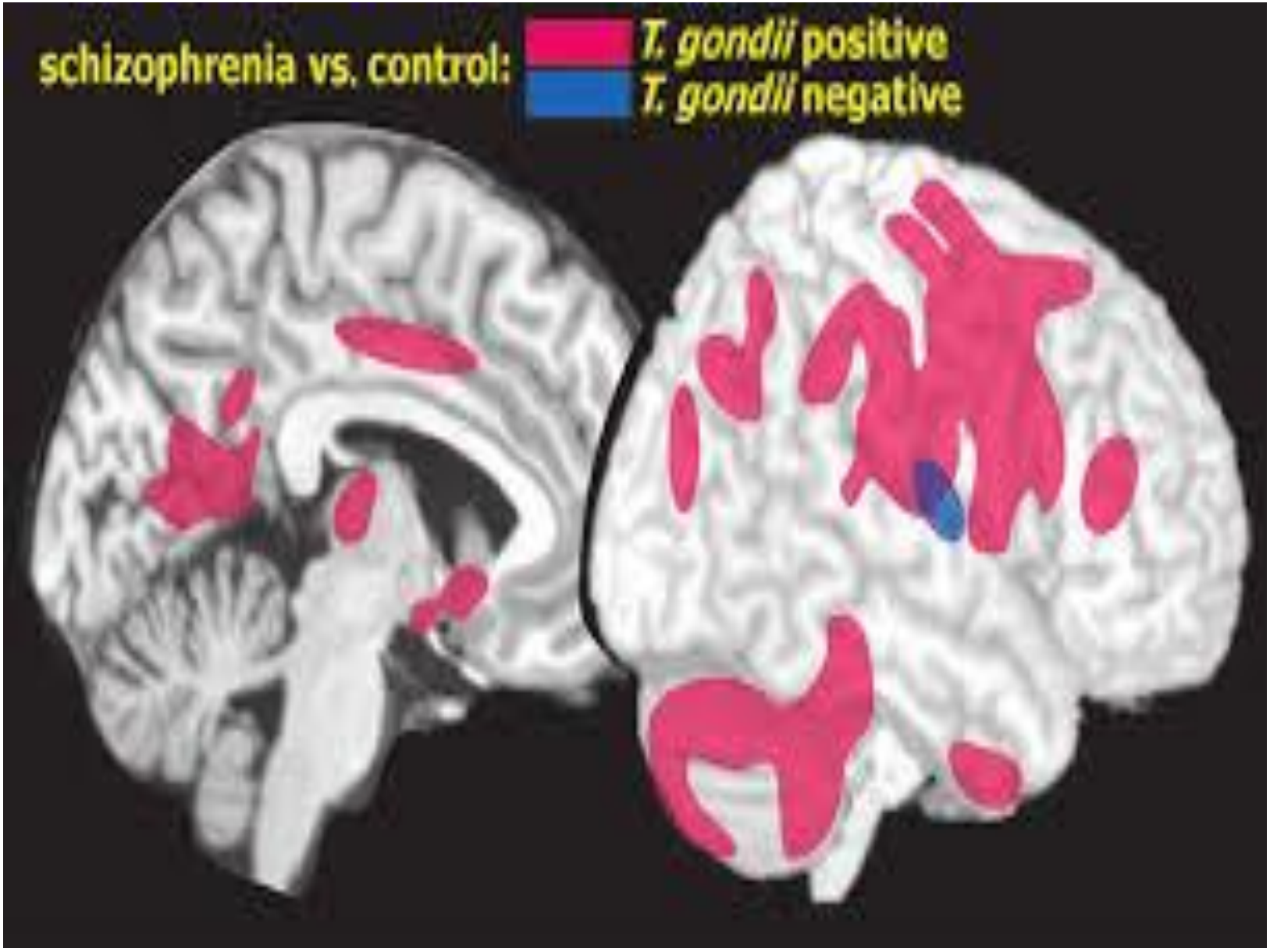
Toxoplasmosis may also be transmitted through solid organ transplants.

Toxoplasma-seronegative recipients who receive organs from recently infected Toxoplasma-seropositive donors are at risk. Organ recipients who have latent toxoplasmosis are at risk of the disease reactivating in their system due to the immunosuppression occurring during solid organ transplant. Recipients of hematogenous stem cell transplants may experience higher risk of infection due to longer periods of immunosuppression.

Heart and lung transplants provide the highest risk for toxoplasmosis infection due to the striated muscle making up the heart, which can contain cysts, and risks for other organs and tissues vary widely.

Risk of transmission can be reduced by screening donors and recipients prior to the transplant procedure and providing treatment.




schizophrenia vs. control:
T. gondii positive
T. gondii negative

Contact with intermediate hosts (dogs and other domestic animals) does not lead to human infection.
A sick person does not secrete the pathogen into the environment and poses no danger to others.
Acquired toxoplasmosis in adults is often asymptomatic.
Most cases of primary infection with toxoplasmosis occur in childhood and adolescence.

Toxoplasmosis can be classified into two categories based on the duration of symptoms and organ involvement.

Classification

Based on duration of symptoms

- **Acute**: If the duration of symptoms is less than 4-6 weeks
- **Chronic:** If the symptoms persist for more than 6 weeks.

The major categories of infection with *T. gondii* infection are:

- **1. Acquired Toxoplasmosis in immune competent individuals;**

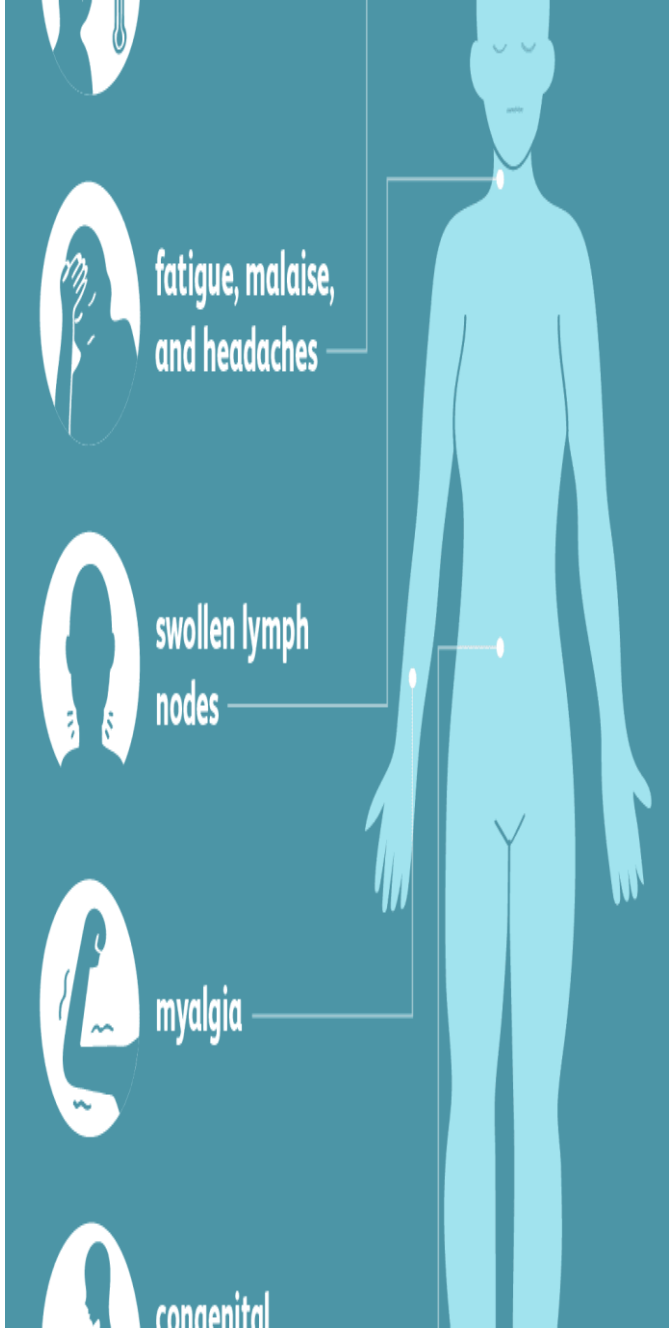
- **2. Congenital Toxoplasmosis:**

- **3. Ocular Toxoplasmosis, which can be acquired or congenital;**

- **4. Cerebral Toxoplasmosis resulting from reactivated infections in immune deficient patients.**

Additionally, recent data suggests that latent infection may lead to neuropsychiatric disease in some immune competent individuals.

Acquired acute infections are asymptomatic in at least 80% of immune competent individuals.
Those with clinical disease most commonly present with lymphadenopathy of the head and neck region; although presentations can also occur involving axillary, inguinal, retroperitoneal and mesenteric lymph nodes.
A single site is usually affected with enlarged nodes from 0.5 to 3 cm in diameter.
Lymphadenopathy may also be accompanied by fever, malaise, sore throat, rash and hepatosplenomegaly.



Acute infection is usually benign and self-limiting.
After 2 to 3 weeks of infection, due to an effective host immune response, tachyzoites are cleared from the host tissues and differentiation into the bradyzoites occurs.
In the chronic phase bradyzoites are found in tissue cysts located primarily in muscular and neural tissue. These cysts persist for long periods of time.
Acute infection, in general, protects the host from symptomatic re-infection. In immune competent hosts chronic infection is typically asymptomatic.
In contrast, in chronically infected individuals with immune deficiency, such as patients with AIDS, reactivation of the latent infection in the brain or other sites can occur.
In reactivation in the brain bradyzoites convert to the actively replicating tachyzoites resulting in necrotizing encephalitis, which can be life threatening.

CLINIC

Incubation Period

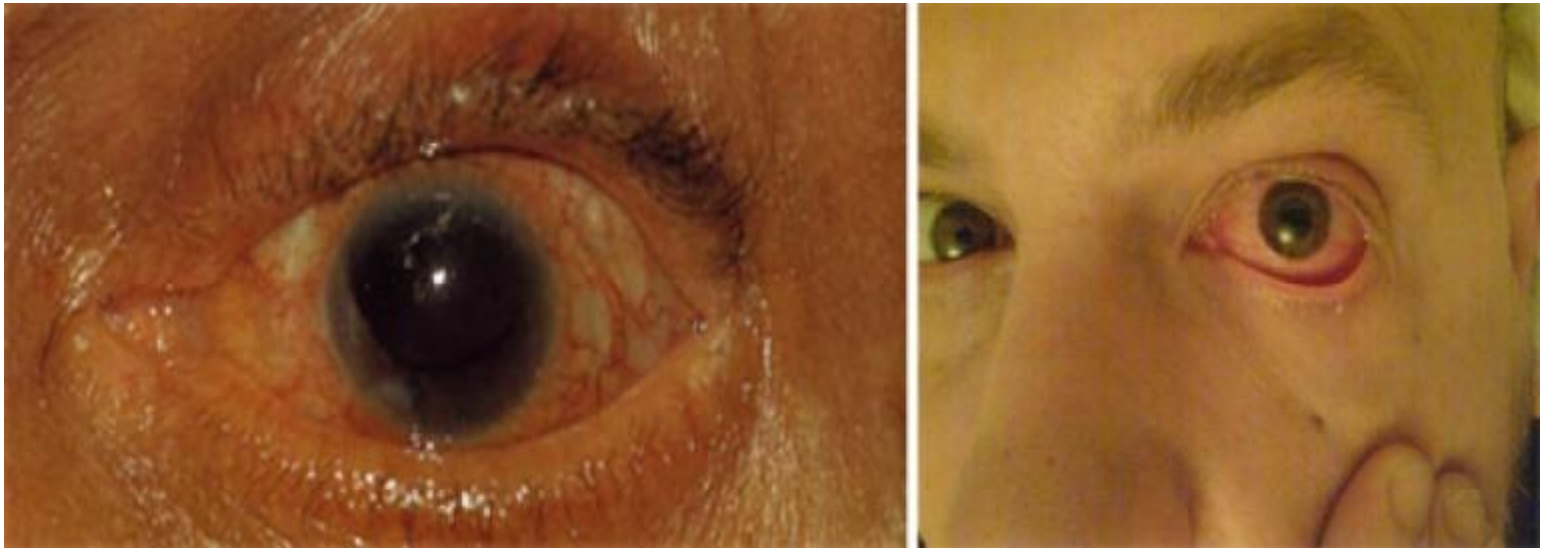
The time between exposure to the parasite and symptom development is 1 - 2 weeks.

Toxoplasmosis: Acquired

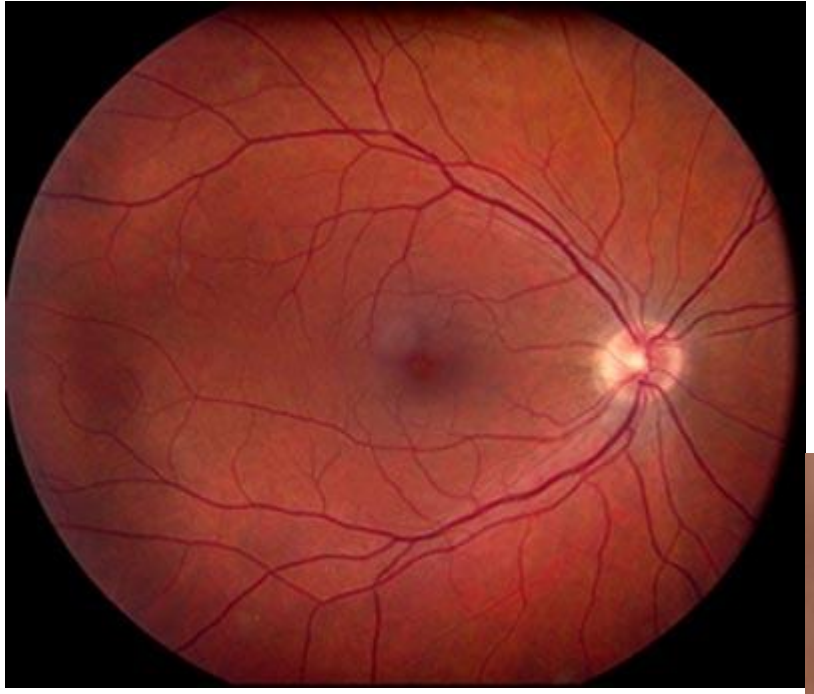
- Headches
- Mialgias
- Pharyngitis
- Hepatosplenomeqaly

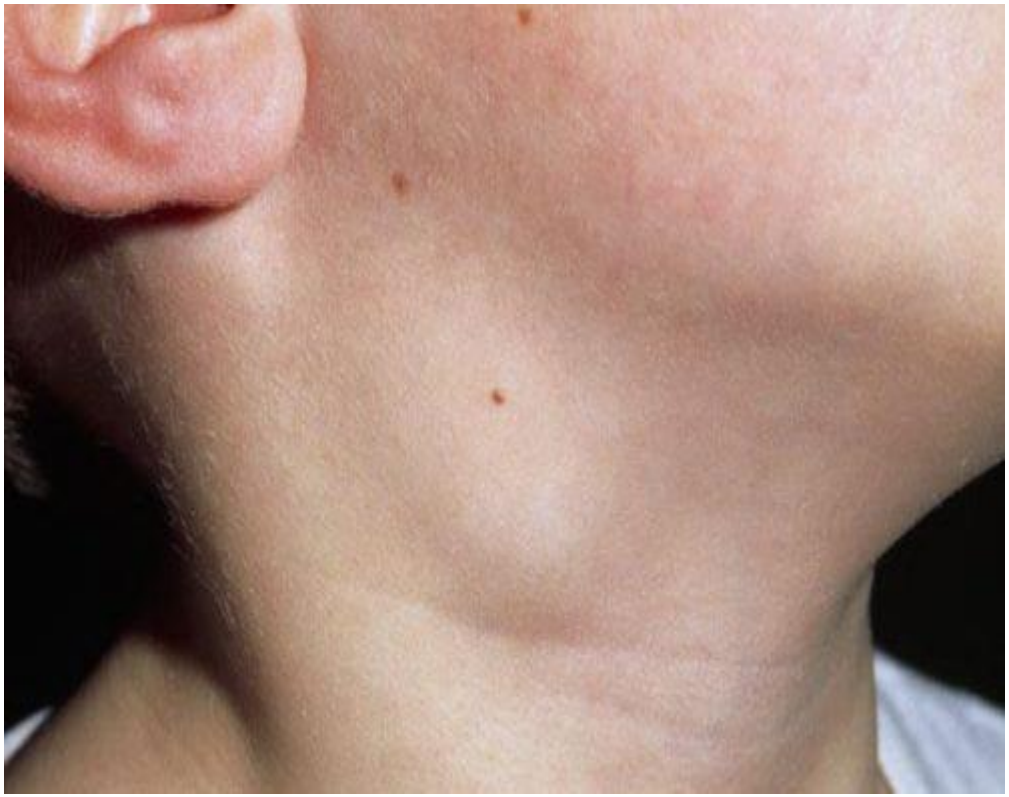
Rare Cases:

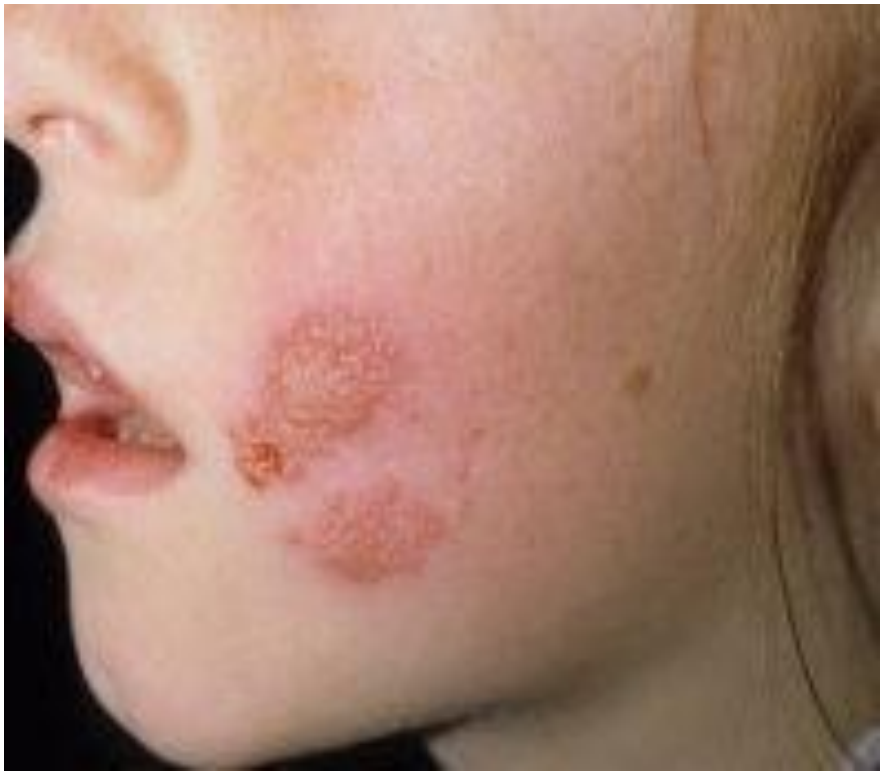
- Pneumonitis
- Miocarditis
- Pericarditis
- Polymyositis
- Hepatitis
- Emcephalitis
- Posterior Uveitis



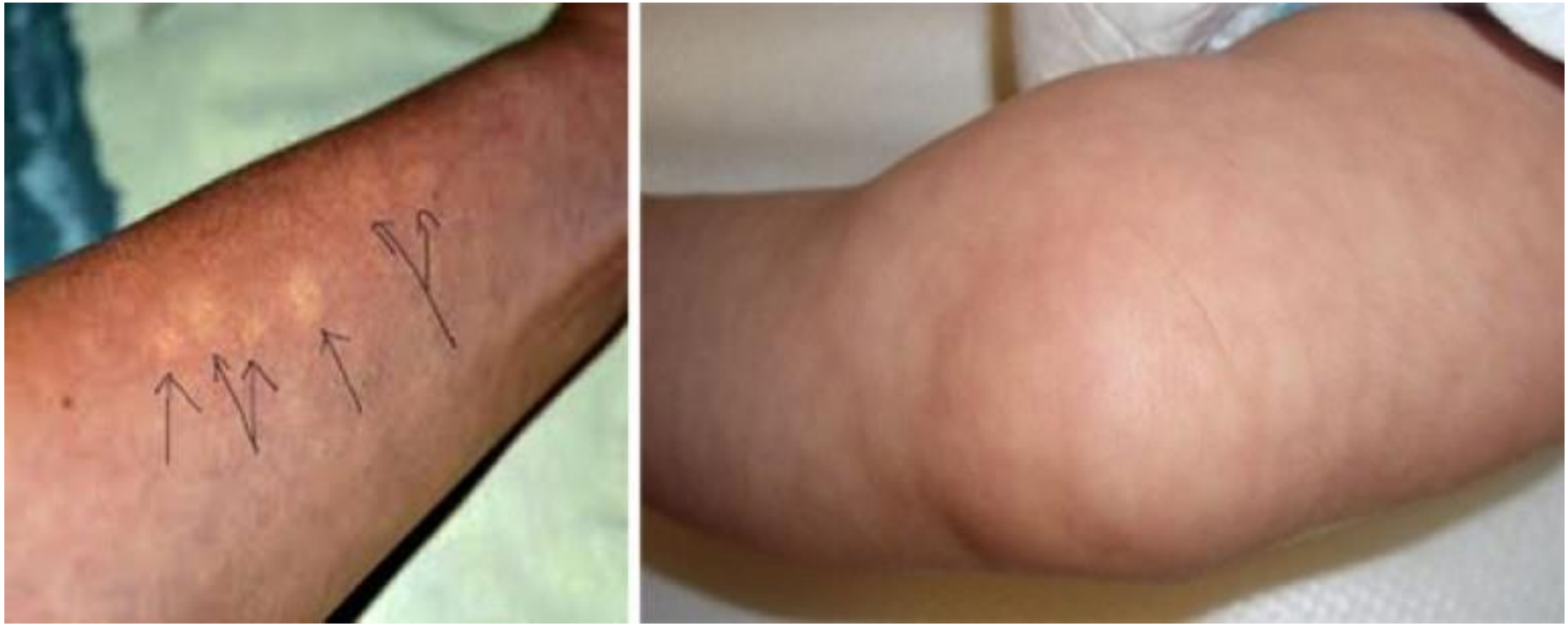
The photo shows conjunctivitis with toxoplasmosis.





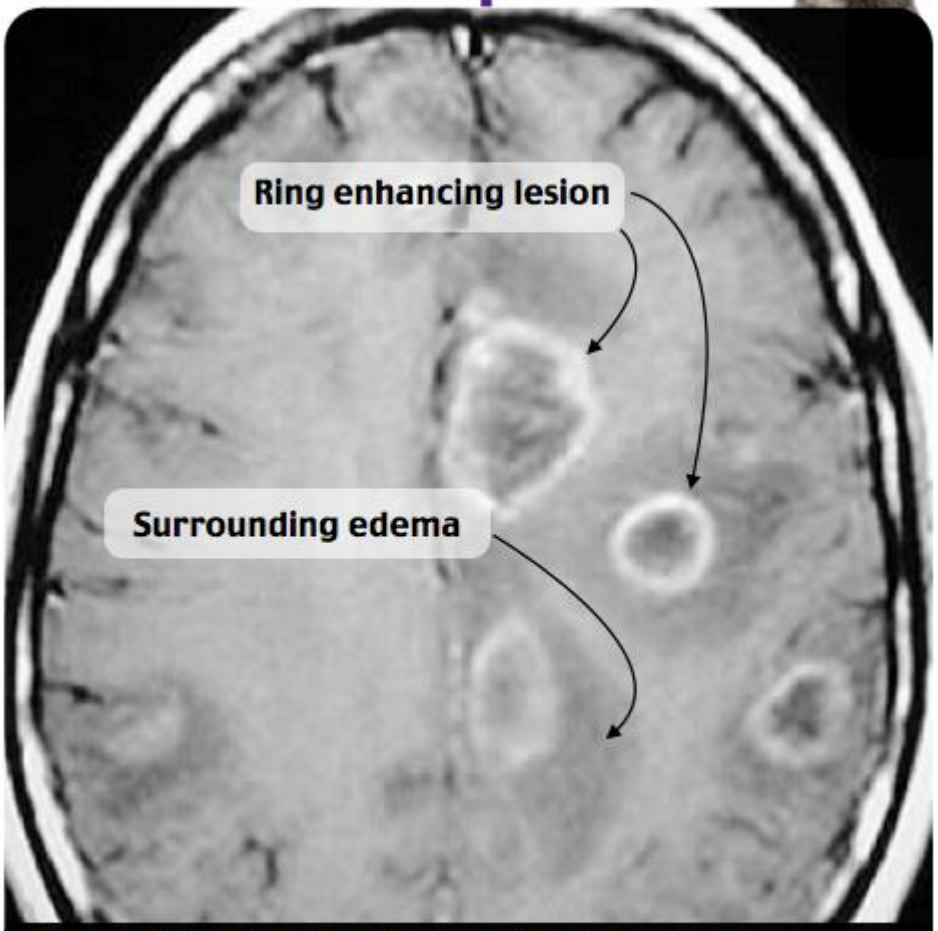


Roseolous-papular rash with toxoplasmosis



In the photo, one of the symptoms of damage to the autonomic nervous system in toxoplasmosis is marbling of the skin.

Cerebral Toxoplasmosis

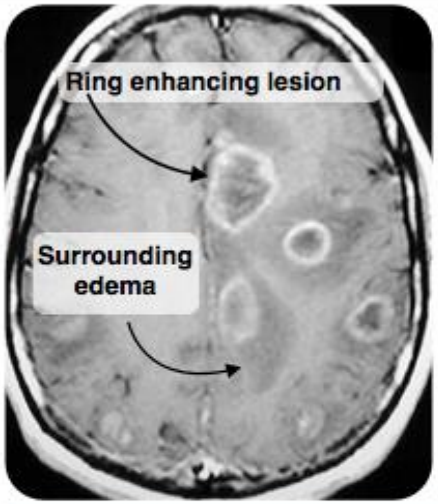


- Most common cause of intracranial mass in HIV
- Headache, fever, AMS, seizure
- Focal neurologic deficits
- Serologic testing not helpful (high antibody prevalence)
- CT: multiple subcortical lesions, ring enhancing lesions with contrast, basal ganglia

Cerebral Toxoplasmosis

Most common CNS infection in patients with AIDS who are not receiving appropriate prophylaxis

Reactivation at CD4 count **< 100 cells/microL**



Clinical
- Headache
- Fever
- Altered mental status
- Seizure

Management

First line
- Sulfadiazine and pyrimethamine
- Leucovorin (co-administer to prevent pyrimethamine-induced hematologic toxicity)

Second line
- Clindamycin plus pyrimethamine plus leucovorin
- Atovaquone plus pyrimethamine plus leucovorin

Toxoplasmic encephalitis

- Toxoplasmic encephalitis is the most commonly reported neurological opportunistic infection.
- The incidence is declining.
- In HIV patients toxoplasma serology may be negative.
- Definitive diagnosis of CNS toxoplasmosis requires the following

1. Compatible clinical findings
2. Identification of one or more mass lesions by CT, MRI, or other radiographic testing
3. Detection of *T gondii* in a clinical sample (CSF) by PCR

Ocular Toxoplasmosis

Immunocompetent adults:

- Unilateral, painless. unifocal
- Vision good if macula not involved

Neonates:

- Congenital toxoplasmosis
- Bilateral, severe
- 70% retinochorioditis
- ⅔ macula involved a/w severe visual loss
- Micorophthalmia, vitritis, glaucoma, ocular palsies

Immunocompromised:

- Bilateral, multifocal, severe
- May be a/w SOL of CNS → Ocular palsies, nystagmus, VF defects

Fetal involvement is most severe when maternal toxoplasmosis is contracted early in pregnancy leading to spontaneous abortion or severe neurological effects. Conversely, infection in the third trimester is often asymptomatic, with development of chorioretinitis commonly occurring later in life.

Congenital transmission occurs almost solely in seronegative women who have acute infection during pregnancy and is not seen in women who are seropositive before pregnancy.

The exception to this rule is the occasional report of congenital transmission in women with immune suppression who have reactivation of latent *T. gondii* during pregnancy.

Congenital Toxoplasmosis

A)Frist

trimester…… Abortion

B)Second

trimester…Stillbirth

C)Third

trimester…Infection

may be present as:-

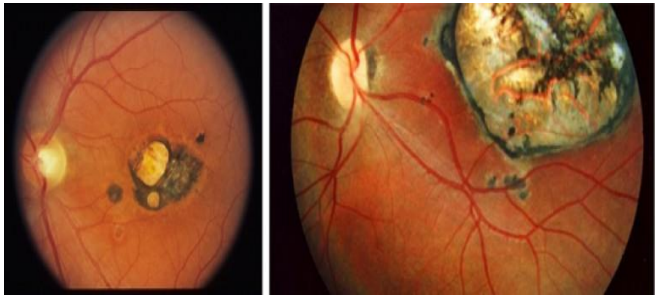
Hydrocephaly,

Neonatal jaundice .

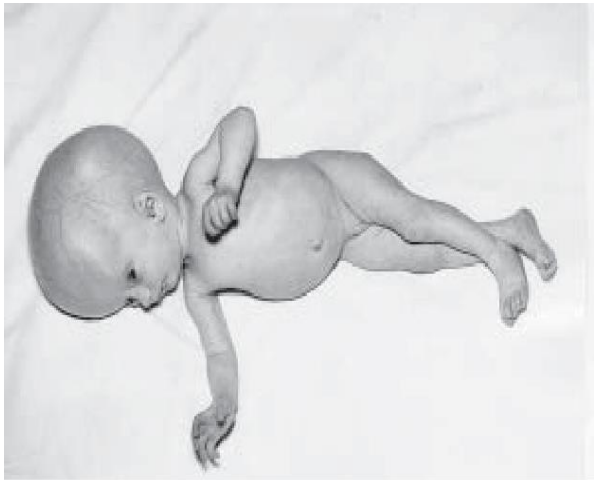
Mental retardation.

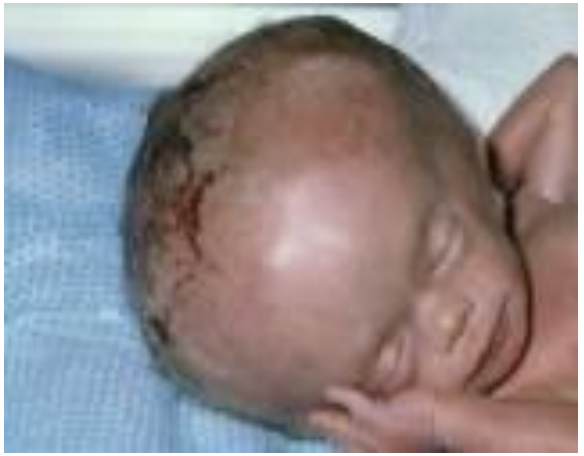
The classic triad of symptoms of congenital toxoplasmosis is

- chorioretinitis,

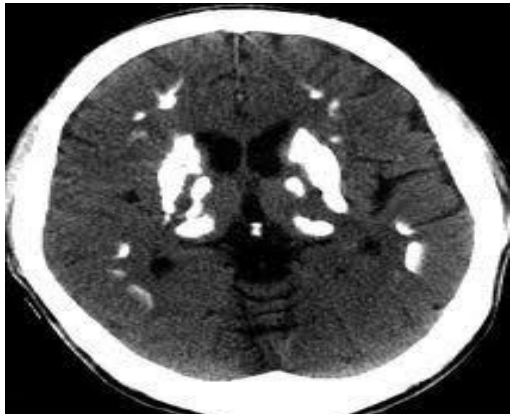


- hydrocephalus, and





- intracranial calcifications, although a variety of symptoms can occur.



Systemic manifestations include

- ✓ **fever,**
- ✓ **hepatosplenomegaly,**
- ✓ **jaundice,**
- ✓ **lymphadenopathy,**
- ✓ **anemia and**
- ✓ **abnormal spinal fluid.**

Other neurologic findings include seizures, bulging fontanelle, with development of serious neurological sequelae such as mental retardation, blindness and epilepsy in infancy or later in life.

Infants infected congenitally often are asymptomatic at birth and subsequently develop retinal disease during childhood

Complications of toxoplasmosis

- **Complications list for Toxoplasmosis:**
- The list of complications that have been mentioned in various sources for **Toxoplasmosis** includes:
- Complications of a pregnant **women** becoming newly infected with toxoplasmosis:
  - Spontaneous abortion - in affected pregnant women
  - Stillbirth - in affected pregnant women
- Fetal or newborn complications of a pregnant woman with toxoplasmosis:
  - Congenital toxoplasmosis - passed to newborn by infected mother by cross-placental contagion.
  - Neonatal jaundice
  - Newborn brain disorders
  - Newborn eye disorders


TXP
TOXOPLASMA
GONDII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MICROWELL ELISA
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IgM (Toxo IgM)
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96 Test
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DIAGNOSTIC AUTOMATION, INC.
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2061 CRAFTSMAN ROAD, SUITE E/F • CALABASAS, CA 91302,
•TEL (818) 591-3030 • FAX (818) 591-8383.

Diagnosis of Toxoplasmosis

Acute toxoplasmosis-

Specimen-

1) Lymph node biopsy
2) Bone marrow aspiration
3)CSF
4)Broncho alveolar lavage
5) Peritoneal fluid

Lab procedure-

1) **Direct microscopy-** Smear is taken in a glass slide→ air dry→ Leishman/ Giemsa stain

- **Findings-** Tachyzoite

2) Culture- Specimen is inocculated in –

- corio-allantoic membrane of embryonated cheek egg/
- lab animal-mice→ incubate→ Observation.

Observation- Bradyzoite.

Laboratory Diagnosis of Toxoplasmosis

1-The detection of *Toxoplasma*-specific antibodies **(IgM & IgG)** is the primary diagnostic method to determine infection with *Toxoplasma*.

2- Observation of parasites in patient specimens, such as bronchoalveolar lavage or lymph node biopsy.

3- Isolation of parasites from blood or other body fluids, and intraperitoneal inoculation into mice or tissue culture.

4- Detection of parasite genetic material by **PCR.**

OTHER LABORATORY METHODS

PCR (polymerase chain reaction)

in blood samples suggest that

- This modality has limited diagnostic value in cases of cerebral toxoplasmosis

CSF (cerebrospinal fluid)

- Is also nonpathognomonic and reveals **elevated protein** and **mild pleocytosis**

SABIN FELDMAN TEST

- Gold stadard test

-Highly sensitive and specific test

-But can not distinguish between recent or past infection

-Antibody detection test

Serology

Sabin Feldman dye test

based on principle that Antibodies to Toxoplasma appear in 2-3 weeks that will render the membrane of the laboratory cultured living T.gondii impermeable to Alkaline methylene **blue ,So the organism are unstained in the presence of serum with antibodies**

CNS Toxoplasmosis-Treatment

Preferred regimen

- Pyrimethamine 2mg/Kg/day for 3 days maximum 25mg, then 1mg/kg/day for 6weeks
- Sulphadiazine 25 - 50 mg/kg/dose QID for 6 weeks

  Plus

  – Folinic acid 5-20 mg 3 times weekly

Alternative regimens

- Cotrimoxazole (15-20mg/kg Trimethoprim plus 100mg Sulfamethoxazole) IV or Oral BD
- Clindamycin (5 – 7mg/kg QID orally) plus Pyrimethamine and Folinic acid

Prophylaxis –Cotrimoxazole prophylaxis

TREATMENT

• **Immunocompetent patients: These patients usually require no therapy if asymptomatic; they may benefit from treatment if symptoms are severe or persist.**

• **Immunocompromised patients: The therapy dosage is *pyrimethamine* (200-mg load, then 50 to 75 mg/day) plus *sulfadiazine* (1000 to 1500 mg every 6 hours) plus *leucovorin (*10 to 20 mg/day).**

The dosage is then decreased to maintenance dosing of pyrimethamine (25 to 50 mg/day) plus sulfadiazine (500 to 1000 mg every 6 hours) plus leucovorin (10 to 20 mg/day) after 3 to 6 weeks if a clinical response occurs.

Alternatives include pyrimethamine, as above, plus leucovorin plus either clindamycin (intravenous [IV] or oral [PO];

600 mg every 6 hours) or atovaquone (1500 mg every 12 hours).

Another alternative is *trimethoprim-sulfamethoxazole* (TMP-SMX) (IV or PO; 5 mg/kg of TMP every 12 hours).

***Corticosteroids* are given only for clinically significant edema or mass effect, and anticonvulsants are given only after a seizure.**

- **HIV patients:**

Start antiretroviral therapy (ART) after 2 to 3 weeks;

stop anti-*Toxoplasma* medications if the CD4 count is greater than 200 cells/mm3 for more than 6 months.

High relapse rate occurs without ART and maintenance therapy.

Acute infection in pregnant women less than or equal to 18 weeks of gestation:

Give *spiramycin* (1 g every 8 hours) until delivery.

**If infection in the fetus is documented or suspected,
or if at greater than 18 weeks of gestation,
give *pyrimethamine* (50 mg every 12 hours for 2 days,
then 50 mg/day) plus sulfadiazine (initial dose 75 mg/kg, followed by 50 mg/kg every 12 hours; maximum, 4 g/day),
plus *folinic acid* (10 to 20 mg/day).**

Before 14 to 18 weeks of gestation, give no pyrimethamine or leucovorin.

- **Congenitally infected infant:**

Give *pyrimethamine* (1 mg/kg every 12 hours for 2 days, then 1 mg/kg/day for 2 or 6 months); then this dose is given every Monday, Wednesday, and Friday;
plus *sulfadiazine* (50 mg/kg every 12 hours) plus folinic acid (10 mg three times weekly) for at least 12 months.

- **Chorioretinitis patients:** **If therapy is clinically indicated, give pyrimethamine (100-mg loading dose over 24 hours, then 25 to 50 mg/day) plus sulfadiazine (1 g every 6 hours) plus leucovorin (10 to 20 mg/day) for 4 to 6 weeks.**
TMP-SMX, one double-strength tablet every 3 days, can prevent relapse.

PREVENTION AND PROPHYLAXIS

- **Avoid undercooked meat and potentially contaminated food or water; clean cat litter daily.**
- **Immunocompromised patients: Give TMP-SMX, one double-strength or single-strength tablet daily. An alternative is dapsone (50 mg/day) plus pyrimethamine (50 mg/wk) plus leucovorin (25 mg/wk).**

If the patient has HIV, start if the CD4 count is less than 100 to
200 cells/mm3; discontinue if the patient is on ART and the CD4 count is greater than 200 cells/mm3 for at least 3 months (primary prophylaxis) or 6 months (secondary prophylaxis).

Recommendation for prevention of toxoplasmosis infection