

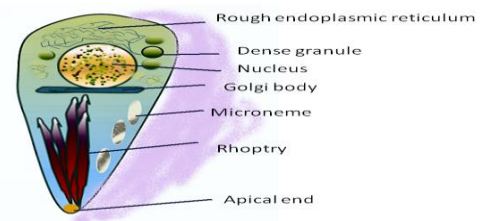
Parasites affecting the central nervous system:

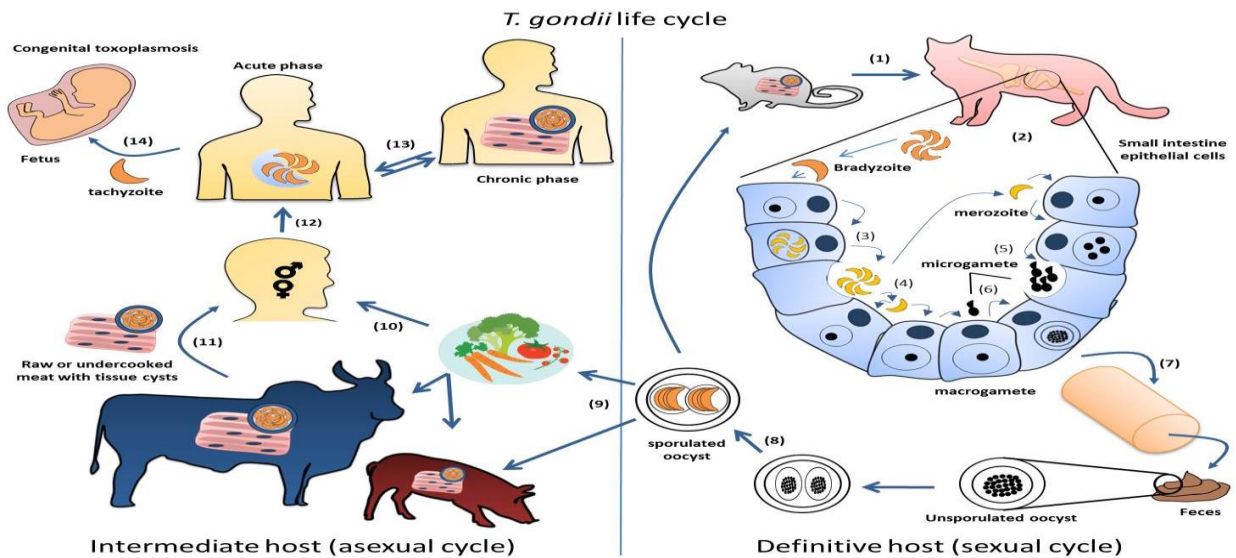
1. Toxoplasma gondii:

- It's a protozoa family member, more specifically a member of the apicomplexa just like plasmodium malaria.
- Causes toxoplasmosis
- Has two reproductive cycles; sexual in the primary host and asexual in the intermediate host
- Divides asexually by a special type of division known as endodyogeny which begins with the division of the nucleus into 2 nuclei inside the mother cell, followed by the development of 2 new cells (2 protozoa) within the mother cell, but eventually, the mother cell will disintegrate & be absorbed by the new protozoa, releasing the 2 organisms, which in turn will repeat the cycle.
- it doesn't divide by binary fission although it's a protozoan.

Morphology:

- small size of 1 micron (easily fitted inside the cells)
- pear shaped protozoan.
- intracellular organism.
- special anterior apparatus (Rhoptry) allowing the parasite to go into the cells & become intracellular.
- it has all the common cell organelles (Nucleus, Golgi apparatus, mitochondria...) including an anterior organelle/ apparatus that helps it to invade the cells & go inside them.





Life cycle:

Primary host: specific, a member of the feline family (domestic cats, wild cats & leopards) but we are more concerned with domestic cats, since these remain in close contact with the human population.

Intermediate host: not specific, toxoplasma gondii can infect many types of cells within the same host & also can infect many types of organisms- hosts (mice, pigs, sheep, cattle, humans, etc.)

The life cycle of the parasite begins with the primary host (cat) ingesting cysts that enter its intestinal cells. Initially, within the cells of the small intestine of the cat, there is asexual division of the parasite but after few divisions the parasite changes into gametocytes, male gametocyte (microgametocyte) and female gametocyte (macrogametocyte), then these gametocytes will fuse forming a zygote that will develop into an oocyst. This oocyst will divide into two sporocysts followed by division of each of these sporocysts into four sporozoites which are excreted in the feces. (Similar to the malaria cycle)

When an intermediate host ingests food contaminated with sporozoites from cat feces, sporozoites will invade the lining cells of the small intestine and it will start dividing within the cell until the cell fills up, ruptures and releases these organisms that can go and infect any type of cells in the host nonspecifically (muscle cells, brain cells, etc).

While they are rapidly & actively dividing within the infected cells, these organisms are known as (tachyzoites). After a while (after filling up the infected cells), these organisms go into a dormant/ quiescent stage (not actively dividing) and are known as (bradyzoites), which will stay inside the infected cell and the cell will produce a lining around them producing a cyst.

The cysts remain in the tissues of the intermediate host until they are eaten by the primary host (cat), then those cysts will rupture releasing the bradyzoites that will change into tachyzoites that will start dividing & invading the lining epithelial cells of the gut and eventually will develop into macro- & micro-gametocytes which will fuse & form the oocysts that are released in the cat feces as mentioned earlier in details.

(Note here that even in the primary host –cat-, there will be an infection & formation of cysts)

Human infection:

- Human is an intermediate host, though considered as a dead end intermediate host, since the life cycle of the parasite ends here (you are unlikely to be eaten up by your pet cat, unless if you're eaten by a tiger :P)
- infection of toxoplasma is usually Asymptomatic
- it is a very common infection however the disease is rare (very rarely, you may have flu-like symptoms that will disappear quickly)
- When infected, the cysts will reside somewhere inside the body cells, but they won't cause any harm since the infection is controlled by the immune system, the patient will be serologically positive (presence of IgG antibodies against toxoplasma Ag)
- Percentage of people serologically positive to toxoplasma ranges between 15%-20% up to 75%, among different populations... regions where you can't find toxoplasmosis –all people are serologically negative- are the regions where there are no cats, like some islands in the pacific ocean.

Infection can be transmitted to humans either by:

- 1) ingesting oocyst of cat feces (eating something that is contaminated with it, as for example when children play with sand that may be contaminated with cat feces having oocysts or when some vegetables are contaminated but yet not well cleaned/ washed before eating them)
- 2) Ingestion of cysts (not oocysts) from undercooked/ raw meat of an intermediate host (sheep, pigs, etc.); since cooking the meat will destroy the cysts... upon eating raw meat, the cyst will release bradyzoites that will change into tachyzoites & again into bradyzoites to form new cysts in the new intermediate host –human-... this method of transmission of infection to humans is the most common.
- 3) Infection can reach the baby when a pregnant woman is infected (transplacentally)

As previously mentioned, toxoplasmosis is common as an infection but rare as a disease & if, however, there's a disease, it'll disappear quickly.

Nevertheless, toxoplasmosis is a problem if the mother got infected with toxoplasmosis for the first time during pregnancy, then the infection can reach the fetus causing congenital toxoplasmosis.

However, if the woman gets infected with toxoplasma without being pregnant & after having the infection, she got pregnant, nothing bad will occur & all her babies will be safe from toxoplasma during all the pregnancies... So, the children will only be affected if the infection for the first time occurs in the woman when she's pregnant.

The earlier the infection occurs during pregnancy the more dangerous it is on the child, if it happens in the 1st trimester of pregnancy, more likely, the fetus will die & will be aborted.

However, if the infection occurred on the 2nd or 3rd trimesters, the baby will survive but will exhibit congenital malformations/ abnormalities (congenital toxoplasmosis), the new born early after birth won't have any symptoms, but after a couple of months, we will notice defects in the central nervous system like mental retardation, neurological deficits affecting sensory or motor functions, also it may lead to partial blindness because only a part of the retina

is invaded. (That's why pregnant women are asked to stay away from close contact with cats)

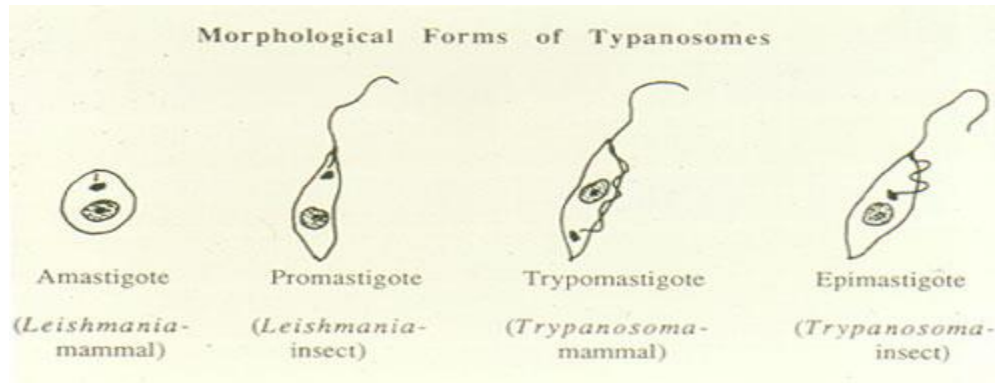
Note that, if the pregnant woman was previously infected with toxoplasma-before pregnancy- & she got infected again during pregnancy, then, her immune system & IgGs will control the infection & prevent the passage of the parasite into the fetus transplacentally.

- ❖ In immunodeficient people when infected for the first time, they will be definitely ill & will exhibit severe symptoms; fever, lymph node enlargement, invasion of the CNS & neurological deficits. However, if you're healthy & you got infected with toxoplasmosis for the first time, most probably there won't be any symptoms, but if after 20-30 years, you became immunocompromised, then there will be **reactivation** (by bradyzoites that will be activated & changed into tachyzoites producing pathology in several parts of the body ... note that when ever you get infected by toxoplasma gondii, you never get rid of the bradyzoites) causing severe symptoms involving the CNS & eyes too.

Diagnosis:

- It's difficult to look for cysts all over the body tissues so we use serological methods.
- Serology: look for IgG antibodies against toxoplasma antigens (can be used for a new born, but we won't check for IgGs against toxoplasma Ags; since they can be the mother's IgGs that crossed the placenta, instead we check for IgM Abs that won't pass through the placenta... if the serology of the baby was positive after birth immediately or even after 6-7 months of birth, this indicates the presence of congenital toxoplasmosis.)

2. Trypanosoma:



- Is of the Trypanosomatidae family.

Trypanosoma exists in two forms, one in the intermediate host (an insect) & another form in the primary host.

Trypomastigote: found in primary host (humans)

Epimastigote: found in intermediate host (fly or bug: tsetse fly or reduviid bug)

Morphological differences:

- in trypomastigote, the undulating membrane extends throughout all the length of the body so that the kinetoplast is present posterior to the nucleus.
- in epimastigote, the undulating membrane only extends one third/ less than half of the length of the body and the kinetoplast is anterior to the nucleus.

There are two types of trypanosome:

- 1) Trypanosoma brucei (causes sleeping sickness) present mainly in Africa
- 2) Trypanosoma cruzi present in south America

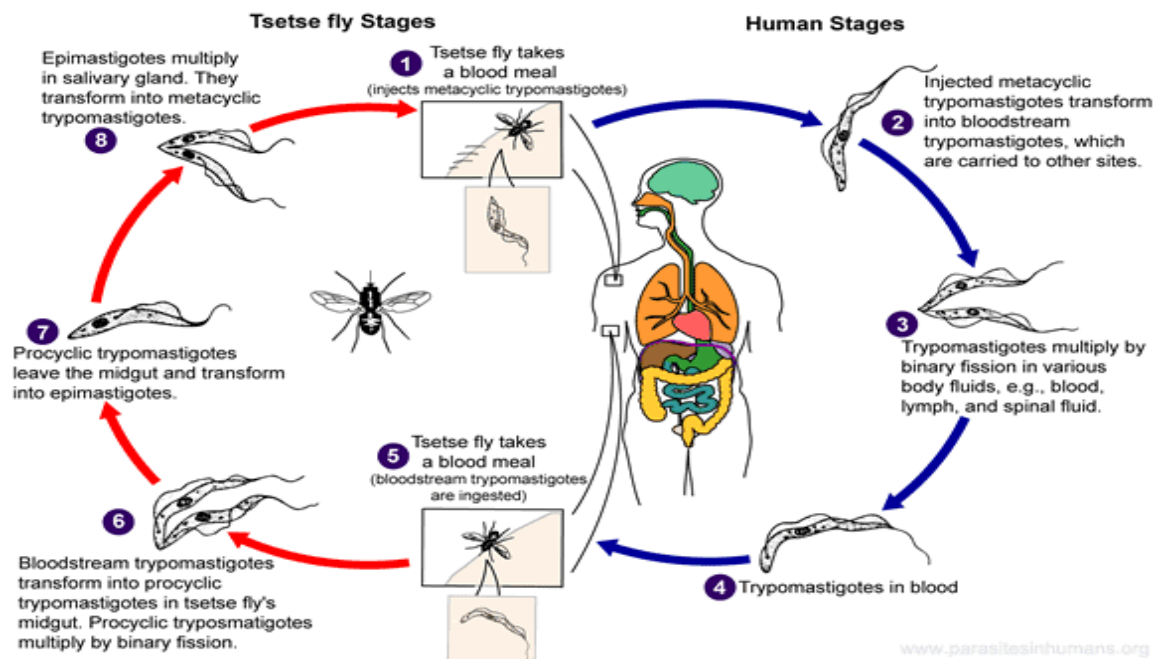
Trypanosoma brucei:

- has two subspecies: *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, they have similar morphology and life cycle, and both cause sleeping sickness.

Trypanosoma gambiense: present in Gambia (central and western Africa)

Trypanosoma rhodesiense: present in Rhodesia (Zimbabwe) (east Africa)

- *Trypanosoma gambiense* is considered as the more prevalent one; causing 95% of sleeping sickness cases.
- East African sleeping sickness (*Trypanosoma rhodesiense*) is more serious, although both infections can be fatal.
- Infection with *Trypanosoma rhodesiense* will kill the patient within 1 year by max if not treated, whereas infection with *Trypanosoma gambiense* is considered more of a chronic condition, less serious, the patient infected can last for a couple of years before eventually dying.
- The vector is tsetse fly and there is an animal reservoir in the case of *rhodesiense*, like cattle & deer in the wild... this is known as “zoonosis”: the disease can affect humans, but it mainly affects cattle & deer in wild, then, the disease will be transmitted from these cattle & deer to humans through the tsetse fly that will bite the cattle & then transmit the disease to humans... note that also the fly can transmit the disease from one human to another human.
- Whereas in the case of *gambiense*, it is possible & debatable that it has a small animal reservoir like pigs, but it mainly affects humans.
- Predominantly humans are the ones infected by sleeping sickness but animals also can be infected & show the manifestations of the disease – sleeping sickness- & die (wild animals are more resistant than domestic animals –which aren’t immune-).
- *Rhodesiense* can be considered as an industrial disease; because once it infects the cattle, it can kill them all and cause an economical loss to the people.



When the Tsetse fly bites a human, it injects the epimastigotes into the blood, which will change quickly into trypomastigotes that will circulate in the blood & go to the lymph nodes, for several months the patient will feel ill & have fever. (Another fly can bite the patient, picks up trypomastigotes that are present already in the blood and then develop into epimastigotes inside the fly, and then the fly in turn bites another host spreading the infection & so on.)

If not treated, the infection will carry on & after several months, trypanosomas will invade the CNS, through crossing the BBB, however, they won't invade the brain itself, but rather will invade the CSF, causing meningoencephalitis & this is the late stage of the disease; which includes symptoms such as: drowsiness, patient detached from his environment, laziness, enlarged posterior cervical lymph nodes, neurological deficits such as: convulsions, paralysis, parasthesia and eventually the patient dies.

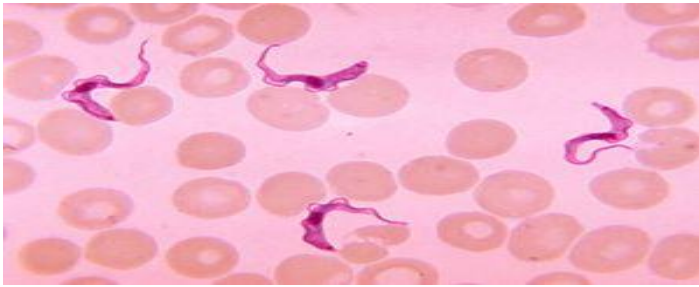
Trypanosoma has the ability of antigenic variability (they can change their antigen very quickly)... The major Ag expressed on the surface is called **vsg** (variable surface glycoprotein of trypanosoma). The patient produces lots and lots of IgM antibodies against these Ags but ineffectively; since that by the time IgM produced is transformed into IgG, the vsg will be changed already. This helps the organism to persist in the host for a long time evading the immune system.

Treating the patient is ineffective in the late stages; however, early during the infection/ disease, the patient can be saved & recovers.

There is a sign known as Winterbottom's sign: it's a sign that's seen in the early stages of trypanosomiasis, when you may suspect the infection, the sign includes mainly the enlargement of the posterior cervical lymph nodes.

Diagnosis:

- 1) Blood smear: trypomastigotes are stained and seen under the microscope.
- 2) Cerebrospinal fluid, where also the trypomastigotes are present.



Trypanosoma cruzi: (American trypanosomiasis)

- Intermediate host is the reduviid bug
- When the bug is infected, it does not inject the epimastigotes into a wound on the host's skin (although the bug bites to feed), but rather, it defecates at the same site with feces containing epimastigotes, when the host scratches the site contaminated by the feces the organism enters through the wound into the blood... this means that if you don't scratch the site of the bite, you won't get the infection.
- In case of trypanosome brucei, the organisms –epimastigotes- are found in the foregut of the tsetse fly, that's why, they're injected into the host through the fly's bite that contains the contaminated saliva... On the other hand, in trypanosome cruzi, the organisms –epimastigotes- are present in the hindgut of the reduviid bug, that's why; they're released in the feces of the bug not in its saliva.
- Can infect the cell intracellularly developing into amastigotes like leishmania
- So, in the primary host (human), it can exist as trypomastigotes in the blood and amastigotes intracellularly.
- Any cell type can be involved (nerve cells, muscles, etc.).

- At the site of the bite (which is also the site of entry of the organism) a swelling known as Chagoma develops... when the bite is near the eyes (usually the bite is on the face) swelling of the eyes develops and is known as Romana sign.
- Most patients will recover & go into a chronic stage of the disease known as (Chagas disease) with no further pathology/ disease, however, they'll serve as a reservoir for people to be infected again.
- A small percentage out of the people going into the chronic stage, will also develop pathological symptoms; these involve the central nervous system, oesophagus, large intestine and the heart (the conductive system will be affected developing conductive pathologies, like branch block, heart block, cardiomyopathies). The patient's oesophagus will lose the peristalsis and it will dilate forming a megaesophagus which will cause regurgitation, difficult swallowing, difficult inhaling and pneumonia & even death. The large intestine will also lose peristalsis and will develop into a megacolon (hugely dilated) causing continuous constipation.

Diagnosis:

- 1) blood smear: look for trypomastigotes
- 2) tissues: amastigotes can be found

3. Taenia solium:

- The only helminth that can affect the CNS.
- Intermediate host is the pig and humans also can be intermediate as well as primary hosts (because pigs have similar tissues to humans)
- Taenia Saginatum doesn't cause any problem in the central nervous system –has nothing to do with it- UNLIKE Taenia Solium.
- If taenia solium eggs – which have striated outer covering and in the middle we have hexacan , the same as taenia saginatum eggs - have been ingested with food contaminated with feces of the same/ another infected person, the eggs will disintegrate and release their hexacans inside the intestines, those hexacans then will invade the intestinal wall into the portal circulation then to the systemic circulation & thus will be

distributed throughout the body developing into cysticerci anywhere in the body, around which there will be an inflammatory process.

- The disease of taenia solium is known as **cysticercosis**.
- Cysticercosis is only found in regions where taenia solium is endemic, fortunately, here in Jordan, it's very unlikely to have cysticercosis (the tapeworm isn't present in Jordan) & if there's an infection with taenia, mostly it'll be taenia saginatum from the cows (the intermediate host of T. Saginatum).
- Since cysticerci can settle anywhere in the body, it may reach the muscles producing an inflammatory reaction, forming painful nodules (in the muscle itself) that are tender in its early stages, but eventually these nodules get calcified after being tender for about 18 months.
- Also, T. solium can settle in the eyes of an infected person damaging the retina and causing blindness.
- Cysticerci may reach the brain tissue & induce an inflammatory reaction around them, followed by fibrosis; damaging the brain tissue & giving rise to neurological deficits that can be motor or sensory... one peculiar deficit is the focal epilepsy.
- Focal epilepsy is epilepsy affecting certain part of the body.
- The occurrence of focal epilepsy in an adult patient with no history of brain disorders should make you suspect Cysticercosis.

Diagnosis:

- 1) Suspect it from the signs and history of the patient.
- 2) CT scans to look for calcified nodules/ lesions.
- 3) Muscle biopsy: look for cysticerci under the microscope.

Good Luck

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