Toxoplasmosis

Introduction\textsuperscript{[1,2]}

Toxoplasmosis is caused by Toxoplasma gondii, an intracellular protozoan parasite. Its main host is the cat. It is one of the most common human parasites. Primary infection is usually subclinical but sometimes leads to chorioretinitis, or may damage the fetus if acquired in pregnancy. Reactivation of latent infection can occur in immunocompromised patients and may cause life-threatening encephalitis.

Life cycle

\textit{T. gondii} oocysts are excreted in cat faeces, mature in the environment and may be ingested by secondary hosts (humans, cattle, sheep, pigs, rodents and birds). In these hosts, there is disseminated infection, which is controlled by the immune response. The active proliferating forms of the organism are called tachyzoites. They can be found in any organ but occur most commonly in the brain, skeletal muscle and heart muscle.

Following a successful immune response, dormant parasites remain encysted in the host tissues for years. They can reactivate if there is immune suppression - notably, AIDS.

The life cycle is completed by cats eating infected animal tissue.

Transmission

Domestic cats are the main source of infection. Infectious oocysts are excreted by the cat for up to two weeks after the initial infection and can survive in warm, moist soil for more than one year.

Humans become infected via the following routes:

- Ingestion/handling of oocysts from cat faeces - via contaminated soil, water or food.
- Eating or handling undercooked or raw meat which is infected - mainly pork and lamb.
- Maternal-to-fetal transmission - occurs almost solely when the primary infection is acquired during pregnancy\textsuperscript{[3]}.
- Organ transplantation - usually in the context of a donor seropositive for \textit{T. gondii} and a seronegative recipient.

Epidemiology

\textit{T. gondii} is worldwide in distribution but the disease occurs less frequently in areas where the environment is unfavourable for the oocysts, such as colder or drier regions and high altitudes. The seroprevalence of populations varies widely - for example:

- A systematic review found that in the USA 16-40\% of the population were infected compared to 50-80\% in South America\textsuperscript{[4]}.
- One study of women attending antenatal clinics in an ethnically diverse population in central London found seroprevalence for \textit{T. gondii} was 17.32\% in 2,610 samples tested\textsuperscript{[5]}.
- About 350 cases are diagnosed in the UK per year\textsuperscript{[6]}.
Presentation

Toxoplasma infections may present in four main ways:

**Acquired infection in immunocompetent adults and children**
- This is asymptomatic in most cases.
- It is said that 10% have symptoms - eg, nonspecific illness or isolated lymphadenopathy (of occipital or cervical nodes, usually resolving within six weeks). However, studies have reported subtle changes in behaviour, personality and psychomotor performance in infected individuals, so the incidence of symptomatic toxoplasmosis may be higher\(^7\).
- Studies suggest a link between toxoplasmosis and schizophrenia\(^8\).
- More chronic lymphadenopathy can occur.
- Rarely, there may be polymyositis, myocarditis, pericarditis, pneumonitis, hepatitis or encephalitis\(^9\).
- Cases of severe, acute disseminated toxoplasmosis in immunocompetent patients, due to atypical strains mainly from the Amazonian rainforest, have been reported\(^10\).

**Ocular toxoplasmosis\(^11\)**
- Toxoplasmic chorioretinitis can occur in both immunocompetent and immunocompromised patients, through acute infection, reactivation or congenital infection.
- Presentation varies:
  - Possible symptoms are reduced visual acuity and floaters.
  - The typical ocular findings are focal retinochoroiditis, a nearby retinochoroidal scar and moderate-to-severe vitreous inflammation.
  - Atypical presentations can occur, such as anterior uveitis, scleritis and optic disc or optic nerve pathologies.
  - Pain is not a common feature (since pain is unusual in chorioretinitis). However, pain may occur in some of the atypical presentations - eg, with scleritis or endophthalmitis.

See also separate Chorioretinal Inflammation article.

**Congenital infection in immunocompetent patients\(^12, 13\)**
- The mother is usually asymptomatic, although some have malaise and lymphadenopathy or rarely chorioretinitis.
- The fetal consequences are more severe if infection takes place within the first ten weeks of conception. The risk of maternal-fetal transmission increases as the pregnancy proceeds but the consequences become less severe\(^14\).
- May cause miscarriage or fetal abnormalities which are detectable on ultrasound.
- May have no apparent symptoms at birth, with complications developing only later in life.
- Neonatal features of infection vary and include hydrocephalus, microcephaly, intracranial calcifications, chorioretinitis, strabismus, severe sight impairment, epilepsy, developmental delay, thrombocytopenia and anaemia.
- The classical triad of congenital infection comprises chorioretinitis, intracranial calcifications and hydrocephalus; however, this is rare.

**Immunocompromised patients**
- Toxoplasmosis can be life-threatening for immunocompromised patients, usually due to reactivation of chronic infection.
- Toxoplasmic encephalitis is the most common feature, with varying presentations\(^15\):
  - It may be acute (eg, acute confusional state) or evolve over days to weeks.
  - Clinical features include confusion, seizures, focal neurological deficits (eg, hemiparesis or dysphasia), cerebellar signs and neuropsychiatric features.
- Other presentations in the immunocompromised are\(^16\):
  - Chorioretinitis.
  - Pneumonitis.
  - Multiorgan involvement with respiratory failure and shock.
Differential diagnosis

- This depends on the clinical scenario.
- With suspected toxoplasmic encephalitis, the differential diagnosis includes central nervous system (CNS) lymphoma, progressive multifocal leukoencephalopathy and other infections (cytomegalovirus (CMV), Cryptococcus spp., Aspergillus spp., Nocardia spp., or bacterial abscess).
- With congenital infection, the differential diagnosis includes rubella, herpes simplex virus, CMV and syphilis.

Investigations

Serology

Clinicians who require confirmation of a case of toxoplasmosis should contact the Toxoplasma Reference Unit based in Wales (telephone 01792 285055; results and general enquiries 01792 285058).

Various tests are available, depending on the type of case (eg, immunocompetent, HIV/AIDS, congenital, organ transplant, ocular infection). They include:

- Reference serology test - IgG and IgM (Sabin-Feldman Dye Test - DT).
- IgM EIA.
- IgM/IgA Immunosorbent Agglutination Assay (ISAGA).
- Molecular Diagnosis (PCR).
- Enhanced Immunohisto-staining.
- Toxoplasma IgG/IgM Immunoblot.

Imaging

- MRI or CT scanning for brain lesions. Typical CNS findings are multiple ring-enhancing lesions. MRI is more sensitive.
- Fetal or neonatal ultrasonography can be used if there is known/suspected transplacental infection. However, the findings are not diagnostic. There may be ventriculomegaly, CNS calcifications, placental changes, hepatomegaly, splenomegaly, ascites and pericardial or pleural effusion.

Trial of therapy

Empirical anti-toxoplasmosis treatment is accepted practice for immunocompromised patients with multiple ring-enhancing brain lesions; patients usually improve within 7-10 days.

Management

There may be life-threatening illness (usually in immunocompromised patients), with encephalitis, pneumonitis, or myocarditis. Patients may require stabilisation and treatment of acute symptoms such as seizures, respiratory failure and cardiovascular compromise. Specific treatment against T. gondii is given, depending on the clinical situation:

Immunocompetent adults and children (non-pregnant)

- Treatment is not usually required unless symptoms are severe, persistent, or incurred through blood products or laboratory transmission.
- The usual drug combination is pyrimethamine, sulfadiazine and folinic acid for 4-6 weeks.

Immunocompromised patients

- For transplant recipients (seropositive donor and seronegative recipient) - trimethoprim/sulfamethoxazole prophylaxis is effective.
CNS toxoplasmosis - combinations of drugs are used - for example:\[15\]:
- Pyrimethamine/sulfadiazine and folinic acid; or
- Clindamycin can replace sulfadiazine if the patient is intolerant; or
- Trimethoprim-sulfamethoxazole for AIDS patients.
- Atovaquone is occasionally used as an alternative to pyrimethamine or sulfadiazine which can be associated with haematological toxicity or allergic adverse effects. It is, however, less readily absorbed and may require novel delivery systems. One study reported the use of a nanosuspension\[25\].

**Treatment** is continued until 4-6 weeks after clinical resolution (may require months of treatment). This is followed by maintenance therapy at lower doses, lifelong or until immunocompetent.

**Maternal and fetal infection**\[26\]

- It is important to distinguish recent versus past infection.
- For recently acquired maternal infection, start treatment as soon as possible.
- There are various treatment regimens, and protocols vary between countries.
- One suggested treatment protocol is:
  - Spiramycin as soon as possible if the fetus is not infected or the status of the fetus is not known (to protect against transplacental infection). This is continued until term, or until fetal infection is documented.
  - Pyrimethamine, sulfadiazine and folinic acid where fetal infection is documented or suspected (e.g., positive amniotic fluid PCR) with monitoring for haemotoxicity. Pyrimethamine should be avoided in the first trimester, as it is teratogenic.
- Alternative drugs such as azithromycin have been used. One study reported good control of *T. gondii* infection in human villous explants\[27\].
- Many protocols also treat the child postnatally; usually for twelve months\[28\].
- Termination of pregnancy may be considered\[6\].

**Immunocompromised, pregnant women with previous infection**\[26\]

- Pregnant women who have HIV/AIDS with a pre-existing *T. gondii* infection risk developing severe toxoplasmosis and/or transmitting the infection to the fetus.
- Fetal transmission in this scenario is rare and there is little evidence regarding prophylactic treatment. Some authors suggest prophylaxis during pregnancy, using trimethoprim-sulfamethoxazole for those with low CD4 cell counts, or spiramycin for those with higher CD4 counts\[12\].
- Despite previous concerns, amniocentesis does not appear to increase the risk of transmission to the fetus, particularly in women receiving antiretroviral therapy (ART), also called highly active antiretroviral therapy (HAART)\[29\].
- Clinical infection in the mother is with either trimethoprim-sulfamethoxazole or pyrimethamine-sulfadiazine. A meta-analysis found there was little to choose between them\[19\].

**Ocular toxoplasmosis**

See separate Chorioretinal Inflammation article.

**Complications**\[30\]

- Nervous system involvement can lead to seizures, developmental delay, deafness or other CNS lesions.
- Ocular disease can lead to visual impairment or, rarely, severe sight impairment.
- Acute infection in the immunocompromised may cause haemodynamic abnormalities similar to septic shock.
- Life-threatening involvement of internal organs (CNS, heart and lungs) - usually in immunocompromised patients.
- Other possible, although uncommon, complications in AIDS patients are panhypopituitarism, diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, orchitis and myositis.
Prognosis

- Most cases in immunocompetent healthy individuals remain subclinical or resolve spontaneously.
- The prognosis in AIDS patients was poor but has improved considerably since the advent of ART (also called HAART)[31].
- The overall prognosis with maternal infection is fairly good[32]:
  - The overall risk of vertical transmission with maternal seroconversion is 26%.
  - Among infected children, 33% have retinal lesion(s) but bilateral visual impairment seems to be unusual; in one survey, no child was severely sight impaired[33].
  - One expert suggested: “the biggest danger to the fetus is not the parasite but the mother’s anxiety.”[32]
- The effectiveness of antenatal and postnatal treatment is still debated[34, 35].

Prevention

Hygiene measures, particularly for pregnant women and seronegative immunocompromised patients[36]:

- Wash hands before handling food.
- Thoroughly wash all fruit and vegetables, including ready-prepared salads, before eating.
- Thoroughly cook raw meats and ready-prepared chilled meals.
- Wear gloves and thoroughly wash hands after handling soil and gardening.
- Avoid cat faeces in cat litter or in soil.

Some countries - eg, France - routinely screen pregnant women for toxoplasmosis. This is not done in the UK or the USA, where prevalences are lower. National Institute for Health and Care Excellence (NICE) antenatal care guidelines and the UK National Screening Committee (NSC) concluded that there was insufficient evidence to recommend screening[36, 37].

Further reading & references

- Toxoplasmosis: diagnosis, epidemiology and prevention; Public Health England
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