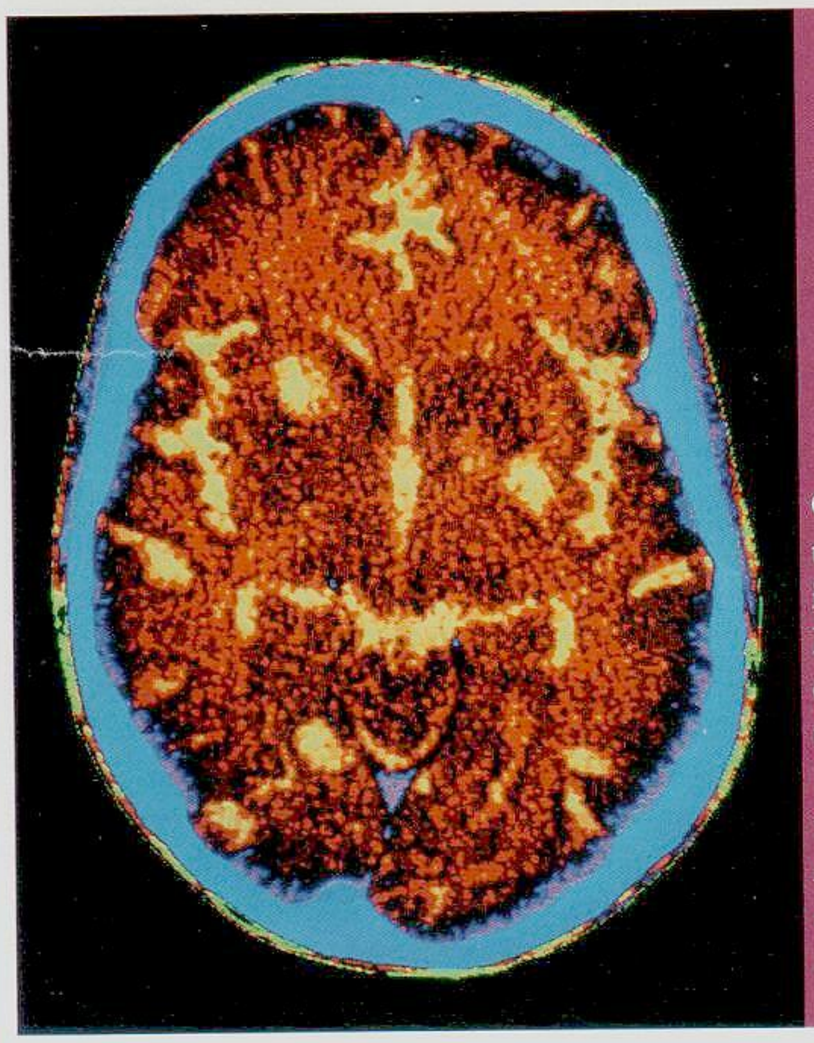
Dr. Bassam Ali Abu Shanab, BPharm, RPh;
Balsam Pharmacy, Tulkarm, West Bank, Palestine

With supplementary information from article by :

Mohammed H Eshmawi, BSc Ph
Assistant OPD Supervisor, King Khalid National Guard Hospital, Jeddah, Saudi Arabia



Cerebral toxoplasmosis in AIDS. False-colour computed tomography (CT) scan of the brain in an AIDS patient suffering from toxoplasmosis.

Toxoplasmosis

Toxoplasmosis is the infection caused by Toxoplasma gondii (a protozoan parasite of the family Sporozoa); an intracellular protozoan, which requires for completion of its life-cycle the definitive host, the cat, and an intermediate host such as a human. Infection of humans occur either by ingestion of foodstuffs contaminated by infected cat faeces, or lamb or pork contaminated with T. gondii cysts or transplacentally (when the mother has an acute infection). However, during immunosuppression, quiescent parasites multiply, resulting in neurologic disease or, more rarely, other organ manifestations.

Note: As two contributors produced good reviews on toxoplasmosis, additional paragraphs or sections of information have been added from the second author in order to produce a single item

Introduction

Toxoplasmosis is an infection found in the tissues of almost all warm-blooded creatures but the only hosts for its definitive life cycle are the cat family. Cats are infected by predation on other infected creatures, or by consumption of oocysts derived from faeces of recently infected cats. T gondii has been shown to be a coccidian that exists in 3 infectious forms: The **tachyzoite** (or endozoite), the **bradyzoite** (or cystozoite), and the **oocyst**.

The importance of the disease lies in its ability to cause transplacental infection with damaging consequences. It is also an important opportunistic infection in acquired immunodeficiency syndrome (AIDS) sufferers.

When the host is infected by oocysts, tachyzoites, or bradzoites, a disseminated infection by tachyzoite forms takes place. The tachyzoites multiply inside the host cells, which rupture when 8-32 tachyzoites are produced. The released tachyzoites infect new cells, but when the immune response controls the infection, some surviving parasites persist for many years in tissue cysts (T. gondii bradyzoites). Tissue cysts can be found in any tissue, but are most common in muscle and brain.

Cats become infected from eating birds, small rodents or other sources of raw meat. Humans and other animals become infected from either oocysts in soil and contaminated food or tissue cysts in raw meat.

Clinical features

There are three major forms of toxoplasmosis:
Congenital infection, acute extrauterine infection (acquired) & toxoplasmosis of the immunocompromised host.

Congenital toxoplasmosis:
Toxoplasmosis acquired in utero can be asymptomatic or may produce signs of disease that can be present at birth. The severity of congenital disease is increased when infection occurs in early pregnancy. The congenital disease is often fatal, and if the infant survives

The history and nature of toxoplasmosis

The causative organism	The parasite Toxoplasma gondii
The first recognition of the disease	First recognized in 1908
The origion of the word Toxoplasma	From the Greek, meaning (shaped as a bow)
The main forms of the parasite life cycle	Oocysts, tachyzoites, and bradyzoites
The primary host	Cats & other felines (oocysts)
The secondary host (all hosts but felines)	T. gondii cells have two forms ; Rapidly multiplying tachyzoites (tachy=rapid) or Dormant, bradyzoites (brady=slow)

the acute infection, he is likely to be handicapped by serious residual CNS and ocular lesions. Clinical manifestations of congenital toxoplasmosis include strabismus, chorioretinitis, encephalitis, microcephaly, hydrocephalus, psychomotor retardation and convulsions, as well as nonspecific manifestations such as anemia, jaundice, hypothermia, thrombocytopenia, diarrhoea, and pneumonitis. The characteristic triad of hydrocephalus, cerebral calcifications and chorioretinitis resulting in mental retardation, epilepsy and impaired vision is the most severe and extreme form of the disease. Cerebral lesions may calcify, providing retrospective evidence of congenital toxoplasmosis.

Acquired toxoplasmosis:
Patients with acquired toxoplasmosis are often asymptomatic, but acute infection in adults may be fatal. Most symptomatic patients present enlarged lymph nodes that are located mainly in the heart and neck area. Malaise and low-grade fever are present in less than 50% of symptomatic cases. Rare manifestations of acute infection include chorioretinitis, myositis, and heart, lung, liver or CNS symptomatic involvement.

Ocular infection (chorioretinitis) occurs if the Toxocara larva becomes lodged in the retina. Death of the organism is associated with a severe uveitis, which may lead to diffuse endophthalmitis. Whitish exudates and fibrosis may occur in the vitreous. Iridocyclitis or cataracts may complicate the course of the disease. [MHE]

Toxoplasmosis in the immunocompromised host:
Toxoplasmosis is a serious disease in patients who are immunocompromised, such as those who have had a transplant or who have AIDS. In transplant patients, the incidence and severity of the disease depends upon previous exposure to the parasite of donor and recipient, the type of organ transplanted and the degree of immunosuppression induced. The disease manifests as a systemic disease with diverse degrees of multiorgan involvement including pneumonitis, carditis, hepatitis, myositis and encephalitis. In patients who have AIDS, the clinical manifestations are usually related to CNS dysfunction or ocular lesions. Myocarditis is frequently found at autopsy, but rarely clinically apparent. Infections of lung and other organs have also been reported.

Epidemiology

Infection rates in humans are very variable and depend upon eating habits and environmental factors. The prevalence increases progressively with age. Toxoplasma gondii cysts are present in 15-30% of lamb and pork meat, and in a much lower percentage of beef. Human disease caused by T. gondii is much more restricted than the infection itself, and is usually a consequence of either intrauterine acquisition or being immunocompromised.

The pathogenicity of T.Gondii and immunity

The tachyzoites of T. gondii invade cells from nearly every organ, where they survive inside parasitophorous vacuoles. Resistance to the infection has been found to be enhanced by interferon (IFN)- gamma and diminished by IL-6. Extracellular tachyzoites are lysed by complement combined to specific antibody and CD4+ and CD8+ T lymphocytes, lymphokine-activated killer and natural killer cells play a major role in infection control.

Diagnosis

1st. Serological tests: immunoglobulin M enzyme - linked immunosorbent assay, latex agglutination, complement fixation test (and haemagglutination test in later eye disease).

2nd. Histological appearance of biopsied nodes.

3rd. Giemsa-stained tissue specimens.

4th. Culture of cerebrospinal fluid or affected tissue (rarely performed).

Serological tests are the mainstay of diagnosis of acquired infection. The Sabin-Feldman dye test, a measure of IgG antibodies, has been widely used. Antibodies can also be detected by indirect fluorescence or indirect haemagglutination. Raised antibody levels are common in the general population and only a rising antibody titre is highly suggestive of toxoplasmosis. The IgM-immunofluorescent antibody (IgM-IFA) test is particularly useful for detecting acute infection since titres rise early and fall rapidly.

T. gondii can be isolated by injecting bone marrow, body fluids or CSF into mice, examining the peritoneal fluid 6-10 days later for the organism. The organism can also be cultured in tissue culture cell lines and T. gondii DNA can be detected by PCR. Patients with eye involvement, those with immunosuppression and those with severe disease need treatment.

The late toxoplasmosis: eye disease
Choroidoretinitis is a late manifestation of toxoplasmosis, and occurs when acute antibody titres have fallen considerably. Dye test and latex agglutination titres of 1:256 to 1:512 (dye test) or 1:128 (latex agglutination) are not uncommon. The haemagglutination test, however, has a slower response to acute infection, and may show significantly elevated titres at the time that eye disease occurs.

Histological diagnosis:
This is the means by which Toxoplasma lymphadenitis is often diagnosed. The histological picture is strongly suggestive of toxoplasmosis. Giemsa-stained tissue smears, myocardial biopsy or brain biopsy preparations can occasionally be shown to contain cysts or typical crescent-shaped trophozoites.

Culture:
Culture of CSF may be used in acute brain infection. This is a specialist procedure, and must usually be prearranged with a reference laboratory. Positive culture can also be obtained from infected placenta, products of conception, CSF and brain in congenital infection.

Toxoplasmosis and pregnancy

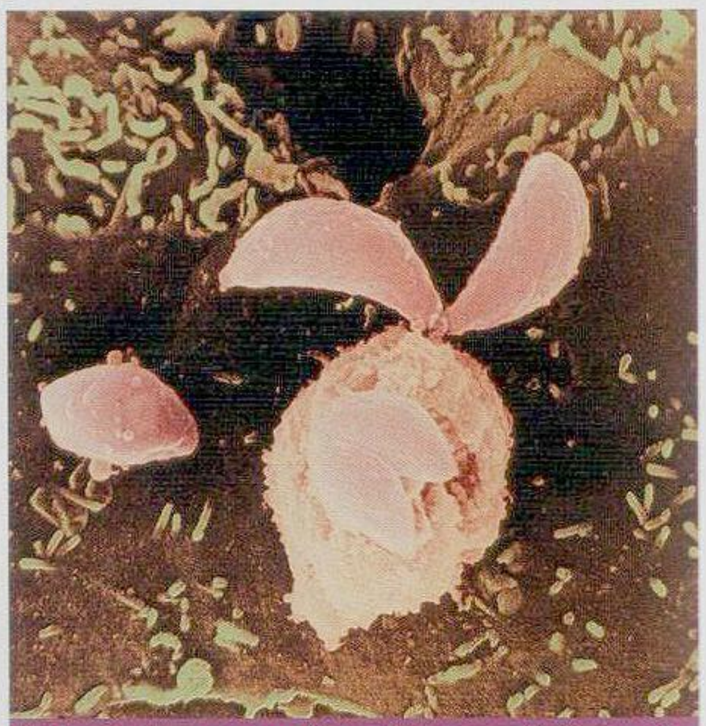
Pregnant women should have their serum examined for toxoplasmosis antibody. Those with negative titres should take measures to prevent infection preferably by having no further contact with cats and not eating raw meats or vegetables that are not thoroughly cooked. T gondii has the ability to cause transplacental infection with damaging consequences. When acute infection occurs during pregnancy, tachyzoites are able to infect the placenta and, in a second step, the fetus.

Prevention

In general, domestic cats that kill mice and birds are the chief source if infection and care should be taken in handling their faeces. Good basic hygiene in the house and garden should be observed.

There are three major levels that can prevent toxoplasmosis:

- To prevent primary infection, the exposure to parasite can be reduced by health education. The main risk factors are eating undercooked (rare) meat & living with a cat.



False-colour scanning electron micrograph (SEM) of Toxoplasma gondii sporozoans leaving an infected cell.

- Maternal immunity due to toxoplasmosis passed before conception protects the fetus from the infection.
- Immunodeficient patients receiving (co-trimoxazole) as prophylaxis for pneumocystis infection are substantially protected from toxoplasmosis.
  No vaccine is presently available.

When acute infection is diagnosed in pregnant women, anti-T. gondii treatment, further assessment of fetal infection and abortion are offered.

Table Recommended treatment for toxoplasmosis [MHE]

Drug	Adult dose	Paediatric dose
Pyrimethamine	25-100 mg/d for 3-4 weeks	2 mg/kg/d for 3 days, then 1 mg/kg/day (max 25 mg) for 4 weeks
+ Sulphadiazine	1-2 g q 6h for 3-4 weeks	100-200 mg/kg/d for 3-4 weeks
Alternative: Spiramycin	3-4 g/d in 4 divided doses for 3-4 weeks	50-100 mg/kg/d for 3-4 weeks
N.B For treatment during pregnancy, continue drug until delivery		

Measures that are recommended to prevent toxoplasmosis:

- Do not eat raw or uncooked meat or eggs.
- While handling raw meat, avoid touching the mouth or contaminating other food; normal hygienic washing of hands and utensils will suffice.
- Cured or smoked meat and sausages are considered safe.
- Wash or peel fruits and vegetables to be eaten uncooked.
- Consume only pasteurized or ultra-heat-treated sterilized milk & diary products.
- Control insect pests and their access to foodstuffs.
- Avoid living with cats; if unfeasible, clean litter trays with nearly boiling water daily.
- Infection in cats can be reduced if they do not use raw meat, birds and rodents as a source of food.
- Use gloves for gardening or handling sand where cats usually defecate.

Treatment [MHE]

Pyrimethamine is a folic acid antagonist. It has a long half-life (approximately 100 hours in adults), thus dosing recommendations vary from daily to every 3 or 4 days. The usual loading dose in adults is 200 mg/day in divided doses. Dosage thereafter may vary from 75 mg to 100 mg/day.

Sulphonamides (sulphadiazine or trisulphapyrimidines) should be used in combination with pyrimethamine to achieve synergistic activity against toxoplasma trophozoites. The sulphonamide inhibitis dihydrofolic acid synthetase. The loading dose of sulphadiazine or trisulphapyrimidines is 75 mg/kg up to a maximum of 4 g, followed by 150 mg/kg/day (up to 8 g/day) in 2 divided doses. Adequate hydration through oral fluid intake should be encouraged to avoid renal crystalluria, with possible renal failure, when sulphonamides are used.

Both of these drugs are folate inhibitors. Folic acid (15 mg twice weekly) should be given. The combination in the high dose given can cause a significant fall in the white cell count. The blood count should be closely monitored during treatment, which must often be continued for 4 weeks or more [BAAS].

Spiramycin is a macrolide antibiotic used frequently for the treatment of pregnant women with acute acquired infection (where sulphonamides are contraindicated). The usual dosage is 2 to 4 g/day in 4 divided doses. Spiramycin is very safe and certainly much less toxic than the combination of pyrimethamine and sulphadiazine.

Clindamycin is given when sulphonamide sensitivity develops in an AIDS patient. The dose is from 1.8-2.4 g/day in divided doses.

Folinic acid (leucovorin) is given orally each day in a starting dose of 10 mg/day. This can be increased incrementally to 50 mg/day if haematologic toxicity develops. Folinic acid may help decrease the bone marrow toxicity of pyrimethamine.

References [BAAS/MHE]

1. Armstrong DC J (1999). "Infectious diseases", Mosby-Year Book, London, ISBN: 0723423288.
2. Bannister BA, et al (1996). "Infectious Disease", Blackwell Science, London.
3. Krupp MA. Chatton MJ (1978). "Current Medical Diagnosis & Treatment", Lange Medical Publication.
4. Kumar P, Clark M (1998). "Clinical Medicine", 4th edition, W. B. Saunders, Edinburgh, ISBN: 070202489.
5. Markell & Voge. "Medical Parasitology", 5th edition: 124-131.
6. Conte JE, Jr. "Manual of Antibiotic and Infectious Disease", 8th edition: 315, 312.
7. Smolin G, et al (1984). "Infectious Diseases of the eye": 171-173.
8. Hope RA, et al (1993). "Oxford Handbook of Clinical Medicine": 208-209.

WORLD NEWS

Aspirin may reduce stroke mortality

Aspirin given within 48 hours after the onset of an acute ischaemic stroke can reduce stroke mortality and decrease disability, according to a joint scientific statement from the American Stroke Association and the American Academy of Neurology published in a recent edition of Neurology. Anticoagulants, however, did not show a benefit.

The statement indicated that for the acute ischaemic stroke patient, evidence shows that there is a slight benefit to giving aspirin early in stroke. They also considered that for prevention of recurrent stroke or prevention of progression or worsening of the stroke, there was not any compelling evidence that heparin, or any of the forms of heparin currently available, are effective. However, combined analysis of available trials found that 160-325 mg aspirin reduced the risk of early recurrent ischaemic stroke when given within 48 h of symptom onset. It showed a small but significant reduction of nine fewer deaths per 1000 treated patients.

Pfizer announce take-over of Pharmacia

The $60bn (£40bn) take-over of Pharmacia & Upjohn will make Pfizer the largest global pharmaceutical company and the first to hold over 10% of the total market. The combined company will have 12 blockbusters (products with annual sales over $1bn), most of which have protection for the rest of the decade.

New antifungal launched in UK

Merck Sharp & Dohme have launched a novel antifungal, caspofungin, for the treatment of invasive aspergillosis who have failed or are intolerant to amphotericin B or itraconzole. Caspofungin belongs to a new class of antifungal, the echinocandins, and inhibits the synthesis of a component of the fungal cell wall, beta (1,3)-D-glucan.