CNS TOXOPLASMOSIS

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Clinical Case

- 42 year old male on 4\textsuperscript{th} month of anti-TB treatment. No other treatment.
- 2 week history of increasing forgetfulness and confusion
- Brought in by wife after he had a generalised fit.
- Clinically post-ictal. No focal signs
CT scan
Management

- $CD_4 -6/ul$
- *Cotrimoxazole 60mg/kg/day for 4 weeks*
- *Valproate for seizures*
- *Patient responded to treatment within a week.*
- *On secondary prophylaxis (cotrimoxazole 1 ds daily)*
- *Will be commenced on HAART shortly*
Epidemiology

- Toxoplasma gondii - obligate intracellular protozoan
- cosmopolitan distribution
- seropositive prevalence rates vary geographically (20-75%).
- Incidence of toxoplasma encephalitis (TE) correlates with prevalence of anti- \textit{T.gondii} antibodies
- Early studies indicate that 24-47% of \textit{T.gondii} seropositive AIDS patients ultimately develop TE
Lifecycle

*Toxoplasma gondii* exists in 3 forms:
- **tachyzoite** - invasive form, rapidly replicating
- **bradyzoite** - tissue cyst, slowly replicating
- **sporozoite** - oocyst
LIFECYCLE OF TOXOPLASMA GONDII

Both oocysts and tissue cysts transform into tachyzoites shortly after ingestion. Tachyzoites localize in neural and muscle tissue and develop into tissue cyst bradyzoites. If a pregnant woman becomes infected, tachyzoites can infect the fetus via the bloodstream.

Diagnostic Stage
1) Serological diagnosis.
or
2) Direct identification of the parasite from peripheral blood, amniotic fluid, or in tissue sections.
Typical Life Cycle

- fertilization within infected host cells of felines
- immature oocysts in feces
- sporulation in environment (1-4 d)

- Ingestion of sporulated oocysts (cat feces + incubation) - thru contaminated vegetables or direct contact with cat faeces
- Ingestion of tissue cysts (bradyzoites) - undercooked pork or lamb meat

- Decystation in gut of intermediate host (man)
- Release of sporozoites and bradyzoites.
- Transform into tachyzoite in enteric submucosa.
- Infect macrophages - rapid replication (tachyzoite stage)
- Dissemination via macrophages to various organs

- In peripheral tissue - control of infection by CMI
- Transform into bradyzoite (slow replicative) within tissue cysts
- Chronic latent infection

Reactivation during immunosuppression
Oral ingestion of oocysts or tissue cysts

Tachyzoite disseminates widely to many organs

Cell destruction with inflammation

Onset of CMI

Transformation into tissue cyst.

Lifelong chronic latent infection

Recrudescence of active infection when there is defective CMI. Presents primarily as TE
CMI in chronic toxoplasma infection

Macrophage

CD154

IL-12

Activated T cell

CD154

NPC

Protects against intracellular pathogens

IFN-δ
Clinical Syndromes

• Congenital infection
  - foetal transmission when mother becomes acutely infected in pregnancy

• Acquired postnatal infection
  - Immunocompetent persons - benign
  - Immunocompromised persons - devastating
Acquired Postnatal Toxoplasmosis

- Benign illness
- 1-2 week incubation period
- acute parasitemia persists for several weeks until development of tissue cysts
- often asymptomatic (>80%)
- common symptom is lymphadenopathy without fever
- occasionally mononucleosis-like (fever, headache, fatigue)
- likely persists for life of patient
- immunosuppression can lead to reactivation
Management of Toxoplasmosis in HIV-Infected Patients

• Primary prophylaxis
  toxo seronegative - preventive measures to avoid acquisition of toxoplasmosis
  Seropositive - chemoprophylaxis to prevent reactivation disease once CD4 is < 200/ul

• Management of Toxoplasma encephalitis

• Secondary prevention:
  Treatment does not eradicate the cyst stage of toxoplasmosis. Therefore maintenance therapy required to prevent relapses.
<table>
<thead>
<tr>
<th>Measures to prevent primary <em>T. gondii</em> infection in immunosuppressed patients.</th>
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</thead>
<tbody>
<tr>
<td>Avoid contact with consumer goods potentially contaminated with cat feces, particularly cat litter and gardening.</td>
</tr>
<tr>
<td>Disinfect cat litter box with near boiling water for 5 minutes prior to handling.</td>
</tr>
<tr>
<td>Cook meat to 66°C or 'well done' or that is not pink in the middle (meat that is smoked or cured in brine may be infectious).</td>
</tr>
<tr>
<td>Wash hands thoroughly after contact with raw meat.</td>
</tr>
<tr>
<td>Kitchen surfaces and utensils that have come in contact with raw meat should be washed.</td>
</tr>
<tr>
<td>Avoid mucous membrane contact when handling raw meat.</td>
</tr>
<tr>
<td>Avoid ingestion of dried meat.</td>
</tr>
<tr>
<td>Wash fruits and vegetables prior to consumption.</td>
</tr>
<tr>
<td>Refrain from skinning animals.</td>
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (PO)</th>
</tr>
</thead>
</table>
| Trimethoprim-sulfamethoxazole | 1 DS tablet daily  
                          | 2 DS tablet 3 times a week                                                  |
| Pyrimethamine*/dapsone  | 50 mg once a week/  
                          | 50 mg daily                                                                  |
                          | 75 mg once a week once a week  
                          | /200 mg once a week                                                        |
Management of Toxoplasmosis in HIV-Infected Patients

- **Primary prophylaxis**
  - Toxo seronegative - preventive measures to avoid acquisition of toxoplasmosis
  - Seropositive - chemoprophylaxis to prevent reactivation disease once CD4 is < 200/ul

- **Management of Toxoplasma encephalitis**

- **Secondary prevention:**
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Clinical Features of toxoplasmosis

- CNS (80% of cases)
- Retina (5-10%)
- Pneumonitis (far less common)
- Myocarditis
- Other organ involvement (in disseminated disease)
Clinical features of TE

- Subacute onset - neurologic and constitutional symptoms progress over days to weeks.
- Fever and headache (40-70%)
- Focal neurologic signs (50-60%) [hemiparesis, cranial nerve palsies]
- Seizures (30-40%)
- Diffuse neurologic dysfunction including confusion and lethargy (40%)
Suggestive Neuroradiologic findings

- Typically contrast-enhancing lesions
- Multiple lesions
- Basal ganglia or corticomedullary location
- Haemorrhage within the lesions suggestive of toxoplastic necrosis
- Surrounding oedema
- Mass effect with ventricular displacement.
Fig. 113.3 Magnetic resonance imaging of the brain in an autologous bone marrow transplant patient with toxoplastic encephalitis (TE). Enhancing lesions are shown (arrows).
Diagnosis

• Empirical Diagnosis
  clinical +
  positive IgG serology +
  radiology (CT/MRI) +
  therapeutic response.

• serological tests: Sabin – Feldman dye test (gold std)/
  ELISA/ IFA
  IgM usually negative.
  IgG positive in 97-100% of HIV-infected patients
  with TE
Diagnosis

Required only for atypical cases or non responders.

- Newer radiology techniques - PET, SPECT
- Histology/ Cytology - demonstration of tachyzoites in tissue biopsies or fluids with surrounding inflammation
- DNA detection by PCR (sensitivity varies from 12-70%, specificity 100%) in CSF
- Culture - (inoculation into mice or cell culture)
Fig. 113.1 Giemsa-stained smear of bronchoalveolar lavage from a bone marrow transplant patient with disseminated toxoplasmosis. Tachyzoite form is demonstrated (arrows).
Fig. 113.2 Hematoxylin-eosin stain of the cyst form of *T. gondii* in brain (arrows).
Toxoplasma tachyzoites in BAL fluid
Diagnosis and Management of toxoplasmosis in HIV+ with neurologic symptoms or signs

CT or MRI

Brain Mass

Toxoplasma IgG +
- Lesion
- Toxoplasma IgG +
  - Antitoxo therapy
    - response
    - Toxoplasmosis

Toxoplasma IgG -
  - Consider biopsy
    - Lymphoma
    - Tuberculoma
    - Cryptococcoma
    - Other tumours

No response
Management of TE

• Empirical approach for:
  
  - positive IgG antibodies
  - CD4 count <100
  - Not on primary prophylaxis or HAART
  - Multiple focal brain lesions on CT or MRI
Less typical Findings should prompt early investigation for alternate diagnosis.

These include:

- Radiology - single lesion, normal MRI.
- CD4 > 100
- Negative serology
- Poor response to treatment
- Patient on primary prophylaxis or HAART
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<th>Drug</th>
<th>Dosage</th>
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<tr>
<td>Pyrimethamine*/sulfadiazine</td>
<td>200 mg loading then 50-75 mg daily PO</td>
</tr>
<tr>
<td></td>
<td>sulfadiazine 1-1.5 g every 6 hours</td>
</tr>
<tr>
<td>Pyrimethamine*/clindamycin</td>
<td>200 mg loading followed by 50-75 mg q24 hours PO</td>
</tr>
<tr>
<td></td>
<td>clindamycin 600-1,200 mg 6 hourly IV or PO</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>10/50mg/kg/day in 3-4 divided doses</td>
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Co-trimoxazole in toxoplasmosis

- Torre et al - Cotrimoxazole vs Pyrimethamine-Sulfadiazine for TE in AIDS (77 patients)
  No difference in clinical efficacy during acute therapy. In contrast, patients on cotrimox appeared more likely to achieve complete radiologic response.

- Francis, Bhigjee et al (Durban) (20 patients)
  Found cotrimoxazole to be effective in acute TE

AAC June ’98 1346-1349
SAMJ Jan 200451-53
Response to treatment

- Neurologic response within 3 days in 50% of patients; 90% by day 14.
- Radiologic improvement by 3\textsuperscript{rd} week of treatment
- Role of corticosteroids
Management of Toxoplasmosis in HIV-Infected Patients

- **Primary prophylaxis**
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- **Management of Toxoplasma encephalitis**

- **Secondary prevention:**
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### Recommended Maintenance Therapy

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<th>Drug</th>
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<tr>
<td>Pyrimethamine*/sulfadiazine</td>
<td>25-50 mg q24 hours/500-1,000 mg q6 hours</td>
</tr>
<tr>
<td>Pyrimethamine*/clindamycin</td>
<td>25-50 mg q24 hours/600 mg q6 hours</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Insert dose</td>
</tr>
</tbody>
</table>
When to discontinue prophylaxis?

- HAART associated with decline in incidence of OIs including toxoplasmosis.
- Observational and randomised studies show that for primary prophylaxis (No previous episode of toxoplasmosis)
  - Can discontinue when CD4 > 200 for ≥ 3 months
- More limited data available regarding stopping secondary prophylaxis (previous episode of toxoplasmosis)
  - Consider discontinuing when CD4 count > 200 for > 6 months and completed initial toxoplasmosis therapy and is asymptomatic
Conclusion

- Toxoplasmosis is the commonest OI causing focal brain disease in AIDS patients.
- Primary prophylaxis has been shown to decrease the incidence of TE in HIV-infected patients.
- Approach to management in patients not on primary prophylaxis or HAART is empirical.
- For resource limited settings the recommended treatment and prophylaxis is cotrimoxazole in appropriately dosed.
Toxoplasma in cat tissues