Cerebral Toxoplasmosis in HIV-Infected Patients

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Infection | Seroconversion | Depletion of CD4 T cells | Death

CD4 T cells $\mu l^{-1}$

- 1000
- 500
- 200
- 0

2–6 weeks | mean of ~10 years

'Flu-like disease (sometimes) | Asymptomatic phase | Symptomatic phase | AIDS

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Introduction

- **Toxoplasmosis:**
  - Caused by the intracellular protozoan, *Toxoplasma gondii*.
  - Immunocompetent persons with primary infection are usually asymptomatic.
  - Latent infection can persist for life.
  - In immunosuppressed patients, especially with AIDS, the parasite can reactivate and cause disease.
Epidemiology

- Seroprevalence rates of toxoplasmosis vary significantly among countries.
- The rate is approximately 15% in the US.
- It is over 50% in some European countries.
Epidemiology

- AIDS patients:
  - In those with CD4 < 100, who are seropositive, there is a 30% probability of developing reactivated toxoplasmosis if effective prophylaxis is not taken.
  - The introduction of anti-toxoplasma prophylaxis and HAART has decreased the occurrence.
Clinical Presentation

- When *T. gondii* reactivates in an AIDS patient, it usually does so in the CNS, leading to cerebral abscesses.
- The most common presenting symptom is headache.
- Other common symptoms include:
  - Confusion
  - Fever
  - Focal neurologic deficits
  - Seizures
Diagnosis

- The majority of patients are seropositive for anti-toxoplasma IgG antibodies.
- Anti-toxoplasma IgM antibodies are usually absent.
- The absence of antibodies makes the diagnosis less likely, but does not exclude the possibility.
Most patients with AIDS will have multiple, ring-enhancing brain lesions often associated with edema.

There is a predilection for involvement of the basal ganglia and periventricular white matter of the brain.

MRI is more sensitive than CT for identifying lesions.
Findings: ring enhancement

T1 post contrast
Cerebral toxoplasmosis
Diagnosis

- The differential diagnosis includes:
  - CNS lymphoma
  - Aspergillosis
  - Tuberculosis
  - Histoplasmosis
  - Syphilitic gummas
Diagnosis

- Toxoplasmosis and CNS lymphoma are the two most common entities.
- Toxoplasmosis accounts for 50% of cases.
- CNS lymphoma accounts for 30% of cases.
Diagnosis

- If these criteria are met, there is a 90% probability of the diagnosis.
  - D4 count < 100
  - Seropositive for T. gondii IgG.
  - Not receiving prophylaxis for PCP & toxo
  - Multiple ring-enhancing lesions.
Diagnosis

- Therefore, it is common to treat empirically.
- If only one brain lesion is detected on imaging, CNS lymphoma rises on the differential diagnosis list, despite positive toxoplasma serology.
Diagnosis

- When to perform brain biopsy or another diagnostic test:
  - If all four criteria are not met.
  - If there is no clinical or radiographic response to empiric therapy.
Diagnosis

- In patients with focal brain lesions already receiving prophylaxis or who are seronegative to T. gondii, PCR testing for other pathogens to be considered, including:
  - EBV
  - JC virus
  - Mycobacterium tuberculosis
  - Cryptococcus neoformans
Diagnosis

- Lumbar puncture may be performed to analyze CSF, which:
  - May have mild mononuclear pelocytosis and elevated protein.
  - With DNA amplification, can detect T. gondii in most patients.
  - When cytocentrifuged and stained with Giemsa, can sometimes show tachyzoites.
ASPERGILLOMA

T2 and DWI of a patient with aspergillosis. There are bilateral foci of patchy increased T2 signal consistent with edema.
Primary CNS Lymphoma positron emission tomography

- Very intense FDG (18 Fluoro-deoxyglucose) uptake in primary brain lymphoma
PML (progressive multifocal leucoencephaophathy)

- Reactivation of JC virus (Papova virus)
- CD4 counts typically < 100
- Subacute evolution of focal disease
- Subcortical white matter disease commonly temporal lobe
- Diagnosis: PCR on CSF for JCV (90%)
Approach to a Patient

Sn's +/- or Sx's of CNS Disease

CD4 >200
Evaluate for Non-HIV Related Diagnosis
- India Ink
- Cryptococcal Ag
- Cytology
- TB culture
- Routine Culture

CD4 <200
Image Brain
- Image Negative
  - LP
- Image Positive
  - Treat for Toxoplasmosis

LP
Approach to a Patient

(Cont)

Treat for Toxo

- Responds
  - Continue RX
- No Response
  - Brain Biopsy
Treatment

- **First-line therapy:**
  - Pyrimethamine 200 mg po loading dose followed by 75 mg/day plus SMX-TMP (10mg/kg) DS BID
  - For sulfa allergic patients, pyrimethamine 200 mg po loading dose followed by 75 mg/day plus clindamycin 600 to 1200IV TID.
  - Clindamycin plus SMX-TMP
  - All pyrimethamine regimens should include folinic acid to prevent drug-induced hematologic toxicity (10 to 25 mg/day po).
Treatment

- Alternative regimens:
  - Used in patients unable to tolerate other medications:
    - Pyrimethamine plus azithromycin (1200 to 1500 mg po qd)
    - Pyrimethamine plus atovaquone (750 mg po qid)
    - Sulfadiazine (1500 mg po qid) plus atovaquone (1500 mg po bid)
Secondary Prophylaxis

- Also known as chronic suppressive therapy:
  - Following six weeks of therapy for treatment of cerebral toxoplasmosis, patients can receive lower doses of medication.

- First choice for treatment:
  - Sulfadiazine 2-4 gm/day divided qid plus pyrimethamine 25-50 mg/day.
  - Folinic acid 10-25 mg/day is given concurrently.
Treatment

- Anticonvulsants:
  - Should be given to patients with a history of seizures.
  - Should not be given routinely for seizure prophylaxis to all patients with cerebral toxoplasmosis.
Duration of Therapy

- For patients who respond, the duration of therapy is typically six weeks at the recommended doses.

- After treatment is complete, the dose of medication can be decreased for secondary prophylaxis.
Steroids

- Adjunctive corticosteroids should be used for patients with:
  - Radiographic evidence of midline shift.
  - Signs of critically elevated intracranial pressure.
  - Clinical deterioration within the first 48 hours of therapy.

- Dexamethasone:
  - Used most commonly
  - Dosed at 8mg TID
  - Tapered over several days
Monitoring of Therapy

- Careful clinical evaluations
- No value to serial assessment of IgG toxoplasma antibody titers
- Radiographic reassessment should be deferred for 2-3 weeks unless there has been clinical worsening or lack of improvement.
Primary Prophylaxis

- Indicated for patients with HIV and CD4 counts <100 who are T. gondii IgG positive.
- TMP/SMX 1 DS 3/w

Patients with negative toxoplasma serology should be counseled to:

- Avoid eating undercooked meat.
- Not to avoid household cats entirely.
Primary Prophylaxis

- If the CD4 count rises above 200 for three months, primary prophylaxis can be safely discontinued.
- If the CD4 drops below 200, prophylaxis should be reinitiated.
Hypocalcemia and AIDS

- Vitamin D deficiency has been found to be a relatively common cause of hypocalcemia in HIV-positive adults.
- Increased incidence of osteopenia and osteoporosis in an HIV-infected pediatric population.
- Association of HIV with calcium homeostasis, resulting in decreased bone density in children.
Hypocalcemia In HIV


Hypocalcaemia in HIV infection and AIDS.

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Abstract

OBJECTIVES: To study the prevalence and possible mechanisms of hypocalcaemia in HIV infection and AIDS.

SUBJECTS: 828 patients with HIV infection or AIDS and 549 controls.

INTERVENTIONS: Measurements of total serum calcium and albumin levels. Parameters of calcium homeostatis were determined in a subgroup of 21 hypocalcaemic AIDS patients.

RESULTS: Mean serum calcium was 2.34 +/- 0.13 mmol L-1 in the HIV group vs. 2.46 +/- 0.10 mmol L-1 in controls (P < 0.0001). After adjusting for serum albumin, hypocalcaemia was present in 6.5% of the HIV group vs. 1.1% of controls. Mean serum calcium was declining according to CDC groups, and differed significantly from controls in each group. Regression coefficients of calcium vs. albumin were 0.147 amongst HIV-infected patients and 0.106 for controls. In the subgroup of hypocalcaemic patients with AIDS, 10/21 had vitamin D deficiency, six of these with low ionized calcium levels. Low serum PTH was found in 2/21 patients. Magnesium deficiency in 1/21. Of the remaining eight patients, only one had secondary hyperparathyroidism, while the other seven lacked an adequate PTH response, despite low ionized calcium levels in four subjects.

CONCLUSIONS: Mean serum calcium concentrations were lower through all CDC stages, irrespective of albumin, resulting in a higher prevalence of hypocalcaemia in HIV-positive patients compared with controls. In a considerable number, this seems to be caused by vitamin D deficiency and potentially a lack of adequate PTH secretion, but further studies are needed to confirm this.
Low PTH In HIV

Various mechanisms including

- Impaired secretion
- PTH resistance.
- Infiltration and destruction of the parathyroid in Pneumocystis or CMV
- Chronic viral infection
- Altered immune function
- Abnormal cytokine production
Summary

Diagnosis of cerebral toxoplasmosis is usually made in

- AIDS patient with a CD4 count < 100
- T. gondii IgG antibodies
- No prophylaxis against pcp & toxo
- Multiple ring-enhancing lesions on brain imaging.
Thank you