Aids Associated TOXOPLASMOSIS

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Durban-Columbia AACTG-ICTU#11210
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University of Kwa-Zulu Natal
Epidemiology

- Toxoplasma gondii - obligate intracellular protozoan
- Seropositive prevalence rates vary geographically (20-75%). Higher in Europe than in USA.
- Incidence of toxoplasma encephalitis (TE) correlates with prevalence of antibodies.
- In 95% of cases - TE is due to REACTIVATION OF LATENT DISEASE.
HIV & TOXOPLASMOsis
EPIDEMIOLOGY

30% probability of developing toxoplasmosis in patients with:
- AIDS, CD4 <100/ul,
- Toxoplasma seropositive
- and not on effective prophylaxis
Aetiology of SOLs in KZN, S.A in HIV-infected persons

- IN DEVELOPED COUNTRIES:
  - TOXOPLASMOsis – 20%
  - PRIMARY CNS LYMPHOMA – 2%
  - MISCELLANEOUS

- IN KZN: PATTERN WAS UNKNOWN
HIV & INTRACRANIAL MASS LESIONS

DEMOGRAPHIC DATA:

<table>
<thead>
<tr>
<th>NO OF PATIENTS: 45</th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENDER</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>AGE RANGE</td>
<td>18 - 56</td>
<td>20 - 43</td>
</tr>
<tr>
<td>MEAN</td>
<td>33.8</td>
<td>25.3</td>
</tr>
</tbody>
</table>
HIV & INTRACRANIAL MASS LESIONS

CLINICAL FEATURES:

- **HEADACHE**: 30/39 (76.9%)
- **SEIZURES**: 20/44 (45.5%)
- **FOCAL SIGNS**: 41/44 (93.2%)
## HIV & Intracranial Mass Lesions

### Total Biopsied/Operated: 38*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>Brain Abscess</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Tuberculoma</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>‘Encephalitis’</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Cryptococcoma</td>
<td>2</td>
<td>5.5</td>
</tr>
<tr>
<td>Infarcts</td>
<td>2</td>
<td>5.5</td>
</tr>
<tr>
<td>No Diagnosis</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

*4 Post Mortem Tissue / 2 ToxO / 2 No Diagnosis*
HIV & INTRACRANIAL MASS LESIONS

‘ENCEPHALITIS’

- NO OF PATIENTS: 7
- NEGATIVE FOR FFG MONOCLONAL ANTIBODIES: CMV, VZV, TOXO
HIV & INTRACRANIAL MASS LESIONS

CONCLUSIONS:

- TOXOPLASMOSIS MOST FREQUENT
- BRAIN ABSCESS IMPORTANT CAUSE
- PCNSL RARE
- PROGNOSIS POOR
Clinical Approach to the Diagnosis of toxoplasmosis
Who is the real McCoy?
35 year old HIV+ policeman presented with R hemiparesis in Sep 2005.
Case 1

- Was on TB treatment from Feb 2005 till Aug 2005

- CD4: 9/ul
- VL: 11580c/ml
- CSF: No cells, chemistry normal, crypto neg
- Started on cotrimoxazole 60mg/kg/day (treatment for toxoplasmosis) for 6 weeks
- Commenced on ARVs (stavudine/3TC/efavirenz) in October ‘05
Referred to me 2 months later with clinical deterioration and seizures
• Was this IRIS or a wrong diagnosis?
• No clinical improvement noted, CD4 11ul.
• Review of results from prev admission:
  • Toxo IgG negative,
  • CSF isolated *M.tb* at 6 weeks
• Liver biopsy on this admission: abundant acid fast bacilli
• Final Diagnosis: Disseminated TB
He improved on a re-treatment schedule (rifafour + streptomycin) and ARVs. Seizures controlled, molluscum contagiosum on face improved, ambulant. 3 months later he presented with recurrence of seizures and severe pain R side CD4: 45/μl, VL <40c/ml
Worsening of cerebral oedema with midline shift

?- IRIS

?- MDR

Susceptibility of CSF isolate: fully susceptible
Repeat CT brain 2 months later
Case 2

40 year old nurse with a prev history of PCP/TB in Oct 2005.
History of allergy to cotrimoxazole
Not on ARVS
Presented in May 2006 with fever and severe headache
CD4:83/ul, VL 2 161 510c/ml
Toxo IgG +
Serum cryptococcal ag Negative
Treated with pyrimethamine and clindamycin
Excellent response . commenced on ARVS 12/Jun/06
Case 3

- 33 year old HIV+ fireman referred to me with a history of primary gastric lymphoma.
- At start of chemo, CD4: 345/ul
- Completed 6 months of chemotherapy.
- Repeat endoscopy: normal
- Referred to me for initiation of ARVs
Case 3

- Complained of severe cough and fever
- Repeat CD4: 104/ul
- CXR: normal
- Reviewed few weeks later, complained of severe headache
- MRI
MRI brain
Case 3

- Toxo IgG negative
- sputum: M.tb isolated on culture
  Commenced on TB treatment (despite normal CXR)
- Brain biopsy: confirmed CNS lymphoma
- Received radiotherapy. Did not respond.
- Died 9 days later
HIV & INTRACRANIAL MASS LESIONS

BRAIN ABSCESS
Diagnosis and Management of toxoplasmosis in HIV+ with neurologic symptoms or signs

CT or MRI

Brain Mass Lesion

Toxoplasma IgG +

Antitoxo therapy

response

Toxoplasmosis

Toxoplasma IgG -

Consider biopsy

- Lymphoma
- Tuberculoma
- Cryptococcoma
- Brain abscess

No response
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
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 palsy]
- Seizures (30-40%)
- Diffuse neurologic dysfunction including confusion and lethargy (40%)
Diagnosis of TE

- Empirical approach for:
- Compatible clinical presentation +
- positive IgG antibodies
  (IgM usually negative, IgG positive in 97-100% of HIV+ patients with TE)
- CD₄ count <100
- Not on primary prophylaxis or HAART
- Multiple focal brain lesions on CT or MRI
Other Diagnostic Modalities

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
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
## Primary Prophylaxis

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dosage (PO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>1 DS tablet daily</td>
</tr>
<tr>
<td></td>
<td>2 DS tablet 3 times a week</td>
</tr>
<tr>
<td>Pyrimethamine*/dapsone</td>
<td>50 mg once a week/</td>
</tr>
<tr>
<td></td>
<td>50 mg daily</td>
</tr>
<tr>
<td></td>
<td>75 mg once a week once a week 200 mg once a week</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<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>
</tr>
</tbody>
</table>
Response to treatment

- Neurologic response within 3 days in 50% of patients; 90% by day 14.

- Radiologic improvement by 3rd week of treatment

- Role of corticosteroids
HIV & TOXOPLASMOsis

COTRIMOXAZOLE

- Cheap
- Easily available
- Used for prophylaxis

What is its role in acute treatment?
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
HIV & TOXOPLASMOsis

COTRIMOXAZOLE

WENTWORTH HOSPITAL STUDY:

BACTRIM® II QID FOR 4 WEEKS

TRIMETHOPRIM 80 mg / tablet 640mg / day
SULFAMETHOXAZOLE 400mg / tablet 3200 mg / day
# Recommended Maintenance Therapy

<table>
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<th>Drug</th>
<th>Dosage (PO)</th>
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</thead>
<tbody>
<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>1 double strength (960mg) daily</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
Extracerebral toxoplasmosis
Clinical Features of toxoplasmosis

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

- Intense, white, focal area of retinal necrosis
- Solitary, multifocal or miliary patterns
- Larger than in immunocompetent individuals and usually no preexisting scar
- Substantial inflammation
Toxoplasmosis chorioretinitis

- Almost always has concomitant CNS involvement
- Reactivation of quiescent tissue cysts in the eye in immunocompromised patients
- Diagnosis on toxo serology – IgG +
- Treatment as for cerebral toxoplasmosis
Toxoplasma tachyzoites in BAL fluid
Fig. 113.1 Giemsa-stained smear of bronchoalveolar lavage from a bone marrow transplant patient with disseminated toxoplasmosis. Tachyzoite form is demonstrated (arrows).
Impact of HAART on toxoplasmosis

• The introduction of HAART and effective prophylaxis has altered the occurrence of TE like other OIs, in North America and Europe.

• In the MAC Study, the incidence of CNS toxoplasmosis decreased from 5.4 per 1000 person-years in 1990 to 1992 to 2.2 in 1996-1998 (after widespread use of HAART)
Whilst there are few natural history studies from resource limited settings, it is anticipated that the incidence of OIs including TE will decrease, now that HAART is part of the HIV/AIDS response in South Africa and other African, Asian and Latin American countries.
Conclusion

• Toxoplasmosis is the commonest OI causing focal brain disease in AIDS patients.
• Primary prophylaxis and HAART have 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 appropriate doses