Inflammatory complications in CNS tuberculosis

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CNS TB

- Accounts for approximately 1% of all tuberculosis cases
- Clinically presents as meningitis, encephalopathy, tuberculomas, abscess
- Associated high mortality and morbidity.
- Prevalent in children and HIV infected individual
- Diagnosis is difficult
- Treatment regimes are not well established
Case 1 (Relapsed disease and drug penetration)

- 33 year old lady, newly diagnosed with pulmonary TB, was due to start her treatment but presented with:
  - Intermittent confusion
  - Bilateral lateral rectal palsies
  - Tongue deviated to the right
  - Finger past pointing and ataxic in gait.

- CT head was normal.

- MRI scan showed TB related demyelination.

- Treated with ATT for 12 months.

- Relapse within few months post treatment

- She was started on RIFATER, MOXIFLOXACIN and PROTIONAMIDE and Dexamethasone.

She has made full recovery, with residual headaches.
Case 2 (Immunomodulation of inflammatory component)

- 24 year old gentleman diagnosed with tuberculous meningio-encephalitis in 2010 in London and had a ventriculo-peritoneal shunt. Continued to have seizures post discharge.

- Bilateral visual loss a year after completing TB treatment

- MRI scan showed extensive lobular enhancing mass in the suprasellar cistern, extending to prepontine cistern- Typical of meningitis. Extensive signal change in the hypothalamus and medial aspect of both temporal lobes- Tuberculoma.

- Persistent pyrexia and raised inflammatory markers

- Suffered from Hypopituitarism due to tuberculoma

- Restarted on TB treatment-changed to RIFATER, THALIDOMIDE and DEXAMETHASONE.

- Repeat MRI scan 6 months after treatment showed reduced basal meningeal thickening and reduced parenchymal oedema.

His symptoms and inflammatory component completely settled.
Case 3  (IRIS)

- 38 year old lady diagnosed with HIV and TB meningitis in Jan 2013.

- Started on TRUVADA, RALTEGRAVIR, SEPTRIN, RIFINAH and dexamethasone.

- Presented in April, May and July 2013 with headache, diplopia, left ptosis and pyrexia.

- With a rising CRP response and lumbar puncture negative for cryptococcal antigen, it was presumed to be TB-IRIS (Immune reconstitution inflammatory syndrome).

**Definition:** A paradoxical inflammatory reaction against a foreign antigen (alive or dead) in patients who have started antiretroviral therapy and who have undergone a reconstitution of their immune responses against this antigen.

Her symptoms improved with steroids and she continued on her HIV and TB treatment.
SUMMARY of 3 cases

Case 1- Relapsed disease most likely due to poor CSF penetration. Use of second line treatment, protonamide and moxifloxacin was important in treating this lady.

Case 2- Poor control of inflammatory responses led to disabilities. Important to start antiinflammatory and immunomodulatory therapy.

Case 3- TB-IRIS is a consequence of treatment for HIV and TB. It is important to continue with TB and HIV drug therapy and start corticosteroid treatment and this should continue until the symptoms resolve.
# Drugs used in treating CNS TB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Est ratio of CSF to plasma Conc</th>
<th>CSF penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAZID</td>
<td>300mg</td>
<td>80-90%</td>
<td>Good</td>
</tr>
<tr>
<td>RIFAMPICIN</td>
<td>450-600mg</td>
<td>10-20%</td>
<td>Poor penetration, maybe high doses will help</td>
</tr>
<tr>
<td>ETHAMBUTOL</td>
<td>15mg/kg</td>
<td>20-30%</td>
<td>Poor penetration once meningeal inflammation settles</td>
</tr>
<tr>
<td>PYRIZANAMIDE</td>
<td>1.5-2.0 g</td>
<td>90-100%</td>
<td>Excellent CSF penetration</td>
</tr>
<tr>
<td>AMIKACIN</td>
<td>15-20 mg/kg</td>
<td>10-20%</td>
<td>Poor CSF penetration</td>
</tr>
<tr>
<td>MOXIFLOXACIN</td>
<td>400mg</td>
<td>70-80%</td>
<td>Good CSF penetration</td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>1000mg</td>
<td>70-80%</td>
<td>Good CSF Penetration</td>
</tr>
<tr>
<td>ETHA/PROTIONAMIDE</td>
<td>15-20mg/kg (max 1g)</td>
<td>80-90%</td>
<td>Good CSF penetration</td>
</tr>
<tr>
<td>LINZEZOLID</td>
<td>1200mg</td>
<td>40-70%</td>
<td>Variable</td>
</tr>
<tr>
<td>CYCLOSERINE</td>
<td>10-15 mg/kg</td>
<td>80-90%</td>
<td>Good CSF penetration</td>
</tr>
</tbody>
</table>

Adapted from Thwaites et al (2013) Lancet Neurology 12: 999-1010
Indonesian investigators have tested the hypothesis that treatment intensification, through use of high-dose intravenous rifampicin and the addition of Moxifloxacin would enhance bacterial killing

IV Rifampicin at 600 mg which is about 13mg/kg was used

Three times increase in plasma and CSF concentration

65% drop in Mortality as compared to 35%

Thalidomide

- Used in the treatment of erythema nodosum leprosum
- Some use in treatment of relapsed CNS TB

**Mechanisms of action**

- Reduces level of TNFα in alveolar macrophages
- Reduction in the size of granulomatous lesions in murine models
- Shown to be a co-stimulator of T cells, increasing IL 2-mediated T cell proliferation and interferon γ production.
Limitations of Thalidomide treatment

- No consensus on the dose or duration of treatment.

- Careful monitoring is required to assess for side effects such as:
  - Peripheral neuropathy
  - Skin rash
  - Hepatitis
  - Neutropenia
  - Thrombocytopenia
  - Teratogenic effects
Protionamide

➢ Bactericidal

➢ Activated form of the drug inhibits the inhA gene product – enoyl ACP reductase.

➢ Usually used as second line therapy, along with another agent as rapid resistance can develop.

➢ Active agonist *M. tuberculosis, M. bovis, M. smegmatis* and *M. leprae*. 
Use of anti-inflammatory therapy in CNS TB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Route of admin</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>2.5 mg/Kg</td>
<td>Intravenous initially, switch to oral when safe</td>
<td>4 weeks, then reduce to stop over 4 weeks</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.4 mg/kg</td>
<td>Intravenous initially, switch to oral when safe</td>
<td>Reducing each week to stop over 6-8 weeks</td>
</tr>
</tbody>
</table>

Adjunctive corticosteroids reduce death and disability by about 30%

Adapted from Thwaites et al (2013) Lancet Neurology 12: 999-1010
Conclusions

Relapse can occur in spite of completing the recommended treatment regime.

When treating CNS TB to consider a combination of drugs with good CNS penetration.

A possibility of using higher IV doses of Rifampicin.

Early use of steroids and immuno-modulators to minimise the inflammatory complications in CNS TB.