Tuberculous Meningitis

Challenges and Opportunities

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Edendale Hospital

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Index patient

- 33 year old male patient, MR N. M.
- Presenting complaint: Three episodes of focal convulsions over previous 27 days: right side of body, thereafter involving entire body, lasting 3-4 minutes, post-ictal confusion and urinary incontinence. Last seizure was 4 days ago.
- Confusion for past 8 days, progressively worsening
- Unresponsive since 19:30 last night as well as febrile
- Further enquiry: non-prod cough one month, LOW, LOA, not investigated for convulsions → phenytoin 2 weeks, headache, no vomiting, no drug ingestion
- PSH: nil of note
- Drugs: Phenytoin 300mg nocte. Nil else
- Allergies: nil known
- Social: sober habits, no travel history, unemployed
- Family history: nil of note
Examination

- General examination: acutely ill, on oxygen and IV fluids anicteric, acyanotic, no pallor, no oedema, no clubbing, oral candidiasis, shotty axillary and inguinal LN, mild dehydration and temporal wasting, no petechiae
- BP 135/89, HR 121, temp 39.4, glucose 5.6, RR 32
- CVS: APPE, tachycardia, regular, undisplaced, no PSH, heart sounds normal
- Chest: RR 32, alar flaring, IC recession, trachea central, equal chest expansion, resonant, diffuse crepitations bilaterally as well as transmitted sounds
- Abdominal: soft, non-tender, normal liver span, no splenomegaly
- Neurological examination: Comatose, no response to verbal or painful stimuli. Incomprehensible sounds, no spontaneous or involuntary movements of any limb. No signs of head injury or bruising. Neck stiffness, pupils were equal, but poorly reactive to light, Fundoscopy: bilateral papilloedema, corneal reflex intact. Oculocephalic reflex intact. Gag reflex was absent. No facial asymmetry. Tone normal, no clonus, brisk reflexes in all 4 limbs, extensor plantar response bilaterally. Unable to assess gait. Examination of back normal.
33 year old Mr. N.M with a background history of PTB and recent onset of focal convulsions with 2° generalization, presents with meningism, deteriorating LOC and ↑ ICP.

In addition, he had signs of immunosuppression as well as aspiration pneumonia.

Considerations - tuberculous meningitis
- cryptococcal meningitis
- toxoplasmosis
- bacterial meningitis
- 1° CNS lymphoma
- Neurosyphilis
Initial Management and Investigations

- Initial management:
  1. endotracheal intubation size 7,5 and T- piece, oxygen
  2. IV access and fluids
  3. u-catheter, NGT
  4. Ceftriaxone 2 gram IVI

- Investigations: FBC, U+E, LFT, CMP, glucose, CXR, CT brain
Investigations

- U+E: Na 133; K 4,1; Cl 108; CO 19; urea 7,6; creat 87
- LFT: TP 88; alb 26; Tbil 11; ALP 54; GGT 122; ALP 54; LDH 1005
- WBC 8,08; abs lymph 1,13; HB 12,9; MCV 79,2; MCH 26,9;
  PLT 201, corrected Ca 2,43, Mg 0,92, glucose 6,42
- u-dipstix: NAD, Toxo IgG: pending, RPR: neg
- CXR: supine, over-exposed, reticulo-nodular infiltrate both upper
  zones, no cavities or LN
- CT: Meningeal enhancement, enhancing lesion in the right basal
  ganglia with mass effect and surrounding oedema. 8mm midline shift to
  the left. The right lateral ventricle and basal
  cisterns are effaced. The left lateral ventricle and temporal horn
  appear dilated.
- ABG: Pa02 80, PaC02 30, pH 7,32, HCO3 17
CT scan
CT scan
Management and Outcome

Management:
- oxygen, IV fluids
- TB treatment initiated
- Dexamethasone
- High-dose Cotrimoxazole
- Ceftriaxone

Outcome:
- Patient unfortunately died within a few hours of admission
Tuberculous Meningitis
Tuberculous Meningitis: Pathogenesis

Macroscopic:
1. Tuberculous bacilli infect alveolar macrophages
   - primary complex
   - bacteraemia and bacilli can seed to the meninges or brain parenchyma forming Rich foci
2. Rupture of Rich focus into subarachnoid space with development of a dense basal meningeal exudate.
3. The following processes can take place:
   - adhesions around interpeduncular fossa → CN palsies 3, 4, 6, 7
   - adhesive exudate can obstruct CSF → hydrocephalus
   - obliterative vasculitis → infarction
   - encephalitis
   - tuberculomas
Pathogenesis: continued

Microscopic:
- Ingestion of inhaled bacilli by alveolar macrophages:
  - Virulence (kat G, rpoV, erp gene) + number of bacilli vs bactericidal activity macrophage (genetic factors influence innate resistance to TB)
- After 2 weeks, T cells specific for mycobacterial peptides appear and two further host responses develop.
  1. Tissue damaging response (delayed type hypersensitivity reaction)
  2. Macrophage activating response (Macrophages process bacillary antigens and stimulate T lymphocytes → release several lymphokines. \(\gamma\) IF enables more efficient intracellular killing. Activated macrophages produce IL 1 and TNF - which promotes granuloma formation)
Pathogenesis: continued

- Rupture of Rich focus → T-lymphocyte dependent response
- Necrotising granulomatous response
- TNF results in enhanced killing of infected cells in vitro, but TNF α concentrations in CSF correlate with clinical progression of TBM in rabbits
Pathogenesis: continued
Clinical features

- Prodromal: low-grade fever (60-95%), headache (50-80%), vomiting (30-60%), irritability, photophobia (5-10%), behavioural changes, anorexia (60-80%), LOW
- Neckstiffness (40-80%), confusion (10-30%), coma (30-60%)
- Neurological complications:
  → CN palsies (30-50%), esp 3,4,6,7 due to adhesions
  → Hydrocephalus
  → Infarcts (10-20%), esp internal capsule, basal ganglia
  → Seizures (adults 5%, children 50%): hydrocephalus, tuberculoma, oedema, hyponatremia
  → tuberculoma
  → TBM with paraparesis: vertebral TB, extradural cord tuberculomas, tuberculous radiculomyelitis
- Hyponatraemia: SIADH, cerebral salt wasting syndrome
Modified British Medical Research Council TBM Severity Grades

Grade I
Alert and orientated without focal neurological deficit

Grade II
Glasgow coma score* 14–10 with or without focal neurological deficit or Glasgow coma score 15 with focal neurological deficit

Grade III
Glasgow coma score less than 10 with or without focal neurological deficit
Diagnosis: Clinical

- High index of suspicion
- Recent exposure to TB (esp children)
- Signs of active extrameningeal tuberculosis
- Thwaites et al developed a diagnostic rule depending on 5 variables. Sensitivity 86%, specificity 79%

However, only 3% HIV+, 23% HIV -, 74% not judged at risk of HIV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&gt;36</td>
<td>2</td>
</tr>
<tr>
<td>&gt;36</td>
<td>0</td>
</tr>
<tr>
<td>Blood WCC (10^3/ml)</td>
<td></td>
</tr>
<tr>
<td>&gt;15000</td>
<td>4</td>
</tr>
<tr>
<td>&lt;15000</td>
<td>0</td>
</tr>
<tr>
<td>History of illness (days)</td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>-5</td>
</tr>
<tr>
<td>&lt;6</td>
<td>0</td>
</tr>
<tr>
<td>CSF total WCC (10^3/ml)</td>
<td></td>
</tr>
<tr>
<td>≥750</td>
<td>3</td>
</tr>
<tr>
<td>&lt;750</td>
<td>0</td>
</tr>
<tr>
<td>CSF % neutrophils</td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>4</td>
</tr>
<tr>
<td>&lt;90</td>
<td>0</td>
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WCC = white cell count. Suggested rule for diagnosis: total score ≤4 = TM; total score >4 = non-TM.
Diagnosis: Radiological

- CT Brain: Basal enhancement, hydrocephalus, tuberculoma, infarction, oedema
- CT and MRI are sensitive to changes of TBM, esp hydrocephalus and basal meningeal excudates, but lack specificity. Differential diagnosis of basal meningeal enhancement include cryptococcal meningitis, carcinomatous infiltration, neurosarcoidosis
**Diagnosis: Bacteriological**

- Thwaites et al: acid fast bacilli: 52%, culture 71%, bacteriological diagnosis 81%
- Meticulous microscopy, culture of large volume
- Culture: Lowenstein-Jensen, Bactec 460
- Typical CSF: predominance of lymphocytes, low glucose concentration, elevated protein concentration. But 10-20% glucose concentration may be normal, protein concentration may be < 0.8 gl/l, Acellular CSF in elderly and HIV+ reported
Alternative diagnostic approaches

Molecular diagnosis
- Meta-analysis of commercial nucleic-acid amplification assays for diagnosis of TBM: sens 56%, speci 98%
- ZN compared with amplified mycobacterium direct test:
  Sens 52% versus 38% before start of TB treatment,
  Sens 2% versus 28% after 5-15 days TB treatment.
∴ ZN better than nucleic-acid-amplification assays before TB treatment is started.

Adenosine deaminase
- ADA produced by lymphocytes + monocytes, sens 82%, spec 83% for TBM (cut-off 11.39 U/L/min), another trial:
  30% of pt with pyogenic meningitis had elevated ADA
Diagnosis of TBM in recent Trials

Definite: - acid-fast bacilli in CSF
  - M. tuberculosis cultured from CSF

Probable: Meningism + CSF abnormalities plus
  - suspected active PTB on CXR or
  - acid-fast bacilli in specimen other than CSF or
  - clinical evidence of other extrapulmonary tuberculosis

Possible: Meningism + CSF abn and ≥ 4 of the following:
  - history of TB
  - duration of illness > 5 days
  - altered consciousness
  - focal neurological sign
  - predominance of lymphocytes in CSF or yellow CSF
  - ratio of CSF to plasma glucose < 0,5
### Treatment of TBM

1. Chemotherapy (BTS and ATS):
   - Intensive phase: INH, RIF, PZA, EMB: two months
   - Continuation phase: INH, RIF: 7 – 10 months

2. Adjunctive corticosteroids

<table>
<thead>
<tr>
<th>Age of patients</th>
<th>&gt;14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC Grade</td>
<td>Grade I</td>
</tr>
<tr>
<td>Drug</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Week 1</td>
<td>0.3 mg/kg/day iv</td>
</tr>
<tr>
<td>Week 2</td>
<td>0.2 mg/kg/day iv</td>
</tr>
<tr>
<td>Week 3</td>
<td>0.1 mg/kg/day oral</td>
</tr>
<tr>
<td>Week 4</td>
<td>3 mg total/day oral</td>
</tr>
<tr>
<td>Week 5</td>
<td>Reducing by 1 mg each week</td>
</tr>
<tr>
<td>Week 6</td>
<td>Reducing by 1 mg each week</td>
</tr>
</tbody>
</table>
Treatment of TBM: steroids

- 1° outcome: Death or severe disability 9 mths after randomisation
- Adjunctive dexamethasone reduced mortality among pts over 14 years of age (relative risk 0.69, P 0.01)
- No significant improvement in combined end-point of death or severe disability after 9 months
- Possible explanations for lack in improvement of morbidity:
  1. Inclusion of pt with possible meningitis
  2. Morbidity endpoint assessed by a questionnaire designed for measuring morbidity of stroke
Treatment of TBM: steroids

- Numbers of HIV infected pt were too small to confirm or reject a treatment effect
- Dexamethasone modulates the production of proinflammatory cytokines and chemokines by microglia cells
3. Thalidomide (TNF α inhibitor)
- Improves survival and neurological outcome in rabbits
- However, trial of adjunctive thalidomide in children with TBM stopped early due to many adverse events (skin rash, hepatitis, neutropenia, thrombocytopenia) and there did not seem to be any benefit from treatment. Not recommended.
4. Neurosurgical intervention
- Non-communicating hydrocephalus: ventriculo-peritoneal shunt
- Communicating hydrocephalus: medical management with furosemide and acetazolamide. Patients who do not respond may have elective ventriculo-peritoneal shunt placement
MDR-TBM

- Prevalence of MDR-Pulmonary TB in SA is 1.6% in treatment-naïve pt and 6.7% among pts who were previously treated for TB
  → 350 with culture pos TBM, 30 pts had MDR-TB (8.6%)
  → susceptibility results often only available after pt died or discharged
  → 7 pt received adequate treatment, 4 of these pts had proven MDR-PTB
  → mortality 56%, remaining sign morbidity
  → 73% prior exposure to TB-treatment,
  10% not previously treated for TB, 17% unknown
Future research

- Increase sensitivity of molecular diagnostic assays:
  Quantitative nested real-time PCR assay
- Rapidly identify MDR-TBM: rapid sensitivity testing using bacteriophages
- Role of adjunctive corticosteroids in HIV+ pt
- Better understanding of pathogenesis: Novel interventions?
- Complete genome sequence of M tuberculosis strain H37Rv has been determined \(\rightarrow\) vaccine design, virulence determinants, mechanisms of drug resistance
References

6. Donald PR. Tuberculous Meningitis. NEJM 2004; 351: 1719-1721
Thank you