Stroke in TB meningitis: Pathophysiology, Clinical & Management issues

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Plan of presentation

- Introduction
  - Stroke & infection
  - Stroke in non CNS TB & TBM
- Pathophysiology
- Prevention
- Hyponatremia
Stroke global burden

- 2nd commonest cause of mortality
- 3rd leading cause of disability \((WHO\ 2012)\)
- In the developing countries
  - Burden of Stroke 70 %
  - Death & disability adjusted life years 87% \((WHO\ 2012)\)
  - Infections important etiology
Population based study 2000-2003 pts Rx for TB without CSN TB (N 2283) Control (N 6849)

IS in TB : 136(6%) Vs control 256(3.7%)

Controlling age, gender, DM, lipids, CA, CAD HR for IS 1.52 (95% CI 1.21-1.91 P<0.001)

TB is a risk factor for IS and not ICH
Experience of pediatric stroke from a tertiary medical center in North India
Jayantee Kalita, Gourav Goyal, Usha Kant Misra*

- 10 y 2001-2011 follow up 79 pts (1 mo-18 Y)
- IS 62(78.5%), ICH 10 (12.7%) CVST 8.9%
- Neuroinfection 25 (31.6%)
  - (TBM 21, Fungal 2, NCC1, HepC1)
- Cardioembolic 9
- Prothrombotic 5
- Arteritis/dissection 4/3
- Mitochondrial 1
- Cryptogenic 13
Stroke in TBM (Rev)

- Stroke in young due to TB vasculitis
  - 8% \( (Dalal \ et \ al\ 1979) \)
  - 19% \( (Thomas \ et \ al\ 1977) \)

- Stroke usually insidious in onset in the background of TBM

- TIA/RIND rare

- Aphasia, agnosia, apraxia & VBI rare

- Stroke associated with x 3 worse outcome \( (Kalita \ et \ al\ 2009, \ Chan \ et \ al\ 2004) \)
Pathology
TBM: pathogenesis

- Tubercles along pial vessels
- 10% primary complex → pneumonia → Miliary TB

Ghon focus
Thoracic duct
Miliary tubercles, tuberculoma, R. Rich's focus
Pathology of TBM

- Exudate
- Hydrocephalus
- Tuberculoma
- Infarct
Stroke in TBM

- Tubercle along pial vessels
- Restriction of tubercular pathology in an arterial territory with a caseous mass in body? Embolic
- Vasculits → Thrombosis
- Hemodynamic changes
Vasculitis in TBM

- Small & medium size vessels → infarction
- Incidence of vasculitis:
  - Autopsy: 41%
  - Angiogram: narrowing 14%, Hydrocephalus 29% (Dalal 1979)
- CT scan: 17-63%
- MRI: 54%
TB vasculitis: pathology

- Tuberculoma in vessel wall rare
- Streptomycin: vasculitis → Fibrous endarteritis with narrowing of lumen
- Exudates α arteritis (Tandon & Pathak 1973)
- ↑caseation in SM Rx cases may contribute
- Reversible narrowing of vessels
- Poor clinical correlation (Wadia and Singhal 1967)
- Stroke from TB vasculitis without meningitis: (Dalal & Dalal 1989)
Pathology and pathogenesis

- Inflammatory infiltration
- Subendothelial protrusion with or without tubercle
- Uniform concentric subintimal proliferation with narrowing of lumen
- Intimal fibrinoid degeneration: leakage of blood in parenchyma

(Dalal 1978)
Infiltration in vessels in TBM 
*(Lammie et al 2009)*

- Media & Advent infilt.
- Fibrinoid nec.
- Artery & vein equally involved.
- Media resistant.
- Response to AFB.
- **Tuberculoma** in adventialiaia > media or intima.
Vascular pathology a function of duration of Rx

- Single or combination
- Duration of illness / Rx determines frequency of changes

Infiltration 2-3 wk

As exudates thickens

Proliferation
- SM cells in intima 11d
- Collagen 45-60 d
- Elastic fibers 16 wk

Necrosis

Infarcts in TBM: hemodynamic
- Vasospasm, intimal proliferation
- Thrombosis
- Stretch
- Strangulation
Poor clinical correlation with angiographic abnormality

- Arterial narrowing without corresponding brain pathology
- Uncommon: organizing thrombus in vascular territory that matches the age of infarct: consider other possibilities e.g. syphilis

“We were impressed by the absence of thrombosis as a factor producing arterial occlusion in TBM “ (Dastur and Lalitha 1973)
Coagulant and fibrinolytic activity in TBM

*(Schoeman et al Pediatr Infect Dis J 2007, 26:428)*

- *Prothrombotic state in pul TB → DVT (Robson et al 1997)*
- 16 TBM children II-III evaluated
  - Anticoagulant (Prot C, Prot S antithrombin)
  - Pro coagulant: Factor VIII, Plasminogen activator inhibitor (PAI), Anticardiolipin antibodies tPA

- **Prothrombotic profile**
  - ↓ Anticoagulant: ↓ Prot S
  - ↑ Procoagulant: ↑ Factor VIII, PAI,
  - N TPA: ↓ Fibrinolysis activity
  - ↑ Platelet count ↑ during Rx (← IL6)

- More marked in stage III than Stage II
- Normalized in 1 st mo of ATT
Pathology and pathogenesis
Clinical features
Radiology
Prevention
Conclusion
Plan of presentation

- Pathology and pathogenesis
- Clinical features
- Radiology
- Prevention
- Conclusion
55/122 (54%) TBM patients had infarction.
- On admission: 42
- By 3 months: 13

Stroke type
- Ischemic 54
- Hemorrhagic tr 7
- Hemorrhage1

(Kalita et al 2009)
Cortical & subcortical infarcts in TBM
Hemorrhagic infarcts in TBM
# Predictors of stroke in TBM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke</th>
<th>No stroke</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\uparrow$BP</td>
<td>6</td>
<td>0</td>
<td>0.007</td>
</tr>
<tr>
<td>-</td>
<td>49</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>9</td>
<td>31</td>
<td>0.001</td>
</tr>
<tr>
<td>II</td>
<td>37</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>30</td>
<td>17</td>
<td>0.001</td>
</tr>
<tr>
<td>Exudate</td>
<td>21</td>
<td>11</td>
<td>0.008</td>
</tr>
<tr>
<td>Prog: Complete</td>
<td>7</td>
<td>29</td>
<td>0.02</td>
</tr>
<tr>
<td>Partial</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>23</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>
Infarcts in TBM associated with poor outcome at 3 mo but not at 6
## Lacunes in TBM & ischemic stroke

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>TBM (n=24)</th>
<th>Ischemic stroke (n=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>♂ 13, ♀ 11</td>
<td>♂ 20, ♀ 4</td>
<td>0.06</td>
</tr>
<tr>
<td>Age (y)</td>
<td>32.62±19.09</td>
<td>54.0±15.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>11</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>6</td>
<td>0.25</td>
</tr>
</tbody>
</table>

(Nair et al Neuroradiol 2009)
### Distribution of lacunes in TBM & IS

<table>
<thead>
<tr>
<th>Region involved</th>
<th>TBM (n=24)</th>
<th>Isch stroke (n=24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate nu</td>
<td>9 (37.5)</td>
<td>2 (8.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lentiform nu</td>
<td>15 (62.4)</td>
<td>13 (54.16)</td>
<td>0.77</td>
</tr>
<tr>
<td>IC Ant limb</td>
<td>5 (20.8)</td>
<td>2 (8.32)</td>
<td>0.42</td>
</tr>
<tr>
<td>IC Post limb</td>
<td>5 (20.8)</td>
<td>7 (29.16)</td>
<td>0.74</td>
</tr>
<tr>
<td>IC Genu</td>
<td>6 (25)</td>
<td>1 (4.16)</td>
<td>0.1</td>
</tr>
<tr>
<td>Ant thalamus</td>
<td>8 (33.3)</td>
<td>3 (12.48)</td>
<td>0.17</td>
</tr>
<tr>
<td>Post thalamus</td>
<td>5 (20.8)</td>
<td>9 (37.5)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Caudate infarct in TBM
Infarction in ischemic stroke: thalamus & post limb of internal capsule
Location of basal ganglia infarct in TBM & ischemic stroke (Hsieh et al 1992)

- **Lacunes**
  - Anterior in TBM in 70.8%
  - Posterior in IS 91.6%

- **TBM:**
  - Medial str.
  - Thalamotuberal
  - Thalamoperforate

- **IS:** Lateral striate vessels

- Posterior location in TBM may be due to coexistence of IS risk factors (Nair et al, Neuroradiology 2006)
Hemorrhagic lesion in TBM

- 32 F, Fever, headache 4 mo
- Alt sensorium 1 mo
- LL weak 1 wk
- Pupils sluggish
- Ppapilloedema
- LL power 2/3
Case report

- CSF
  - Cells = 400 (P-60%, ly-40%)
  - Protein = 495 mg/dl
  - Sugar = 21 mg/dl (80 mg/dl RBS)

RHZE

- 2 mo sudden worsen
  - ? Hydrocephalus
  - ? Stroke
TBM with hydrocephalus, arachnoiditis & ICH
## Aneurysm or hemorrhage in TBM

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Age/sex</th>
<th>Site aneurysm</th>
<th>ICH</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 1951</td>
<td>??</td>
<td>??</td>
<td>-</td>
<td>Clsoe TBculoma</td>
</tr>
<tr>
<td>Suwanweb 1972</td>
<td>22F</td>
<td>BL ACA, R MCA, L PCA</td>
<td>=</td>
<td>Ca, infl exudate</td>
</tr>
<tr>
<td>Whelan 1981</td>
<td>??</td>
<td>L MCA rrifurcation</td>
<td>-</td>
<td>Clsoe Tbculoma</td>
</tr>
<tr>
<td>Leguarda 1988</td>
<td>&lt;14</td>
<td>MCA horizontal part</td>
<td>-</td>
<td>Infl exudate</td>
</tr>
<tr>
<td>Gupta 1994</td>
<td>24 M</td>
<td>MCA</td>
<td>-</td>
<td>Infl exudate</td>
</tr>
<tr>
<td>Griffith 2000</td>
<td>9 M</td>
<td>PCA</td>
<td>SAH, IVH</td>
<td>Ifl exudate</td>
</tr>
<tr>
<td>Tsuboi 2000</td>
<td>55F</td>
<td>MCA</td>
<td>SAH, IVJ</td>
<td>Blod in infl</td>
</tr>
<tr>
<td>Yashoe et al.</td>
<td>50 F</td>
<td>SAH</td>
<td>Blod in infl</td>
<td></td>
</tr>
</tbody>
</table>
N67 age 34 (3-75): Abn 61(91%)

MRA abnormal in 34(50%)
- MCA 21, PCA 14, ICA 8, ACA 8, Basilar 5, vertebral & sup cerebellar 1 each
- Corresponding infarct 61.8%
- Abn both ant & posterior territoriae 25%
- MRA abnormality related to Hydrocephalus & infarct

Infarction at 3 mo : abn MRA 47%
TBM MRA clinical correlation

- 21y M TBM
- Narrow PCA, MCA, ACA
- Infarct OCC
- BG BL
36 y M TBM stage II
R MCA narrowing
R PCA occlusion
Corresponding infarct

14y M TBM stage III
R PCA occlusion
Parito occipital Infarct & R frontal
Pt died at 5 mo
Case report

- 22y ♀ TBM stage II
- RICA, PCA, ACA block
- Infarction in Parito occipital & cerebellar
Clinical & MRA correlation

- 30Y♂ Stage III TBM
- Cortical & BG infarct in MCA territory
- MRA normal
## Angiographic findings in TBM

<table>
<thead>
<tr>
<th>Author</th>
<th>Rojas Echeverri 96</th>
<th>Gupta 94</th>
<th>Gupta 79</th>
<th>Leeds 71</th>
<th>Airon 91</th>
<th>Kalita 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessels narrow/occluded</td>
<td>46</td>
<td>50</td>
<td>48</td>
<td>100</td>
<td>93</td>
<td>110</td>
</tr>
<tr>
<td>ICA</td>
<td>8%</td>
<td>50%</td>
<td>4%</td>
<td>40%</td>
<td>93%</td>
<td>23.5%</td>
</tr>
<tr>
<td>MCA</td>
<td>42%</td>
<td>40%</td>
<td>44%</td>
<td>60%</td>
<td></td>
<td>62%</td>
</tr>
<tr>
<td>ACA</td>
<td>33%</td>
<td>15%</td>
<td></td>
<td></td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>PCA</td>
<td>13%</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
<td>41%</td>
</tr>
<tr>
<td>Modality</td>
<td>DSA</td>
<td>MRA</td>
<td>X-angio</td>
<td>X-angio</td>
<td>X-angio</td>
<td>MRA</td>
</tr>
<tr>
<td>Pts N0</td>
<td>24</td>
<td>20</td>
<td>50</td>
<td>5</td>
<td>14</td>
<td>67</td>
</tr>
</tbody>
</table>
Case report
50y♀: fever 1mo, drowsy paraplegia 15 d

- CSF: protein 495mg%, 100l/mm3 sugar 30(121) mg/dl
- D2: RHZE
- D5: Asymmetric pupil : herniation
- D6/D 7: EVD → revised
- D8 Mechanicalventialtion
- D10: Ext posturing deep coma
- D30: GI bleed, DIC & VAP
- D41 VP Shunt
Worsening after shunt

- **CSF over drainage:**
  - ICH / SDH ↓CSF buoyancy →
  - Traction on vessels
  - Hemispheric shift & infarct
  - Due to CSF overdrainage

- **EVD over drainage** → Lumbar pressure upward herniation

(Adams et al 2007)
Preventing stroke in TBM

- Corticosteroids
  - ↓ mortality & ↑ outcome
  - But not the frequency of stroke/hemiplegia

- Aspirin
  - Anti inflammatory
  - Antiplatelet
  - Antioxidant
  - Used for stroke prevention

- Aim
  To evaluate the role of aspirin in preventing stroke in TBM
Role of aspirin in TBM
Effect of aspirin, mortality & outcome in TBM at 3 mo

- Mortality
- New stroke
- Complete recovery
- Partial recovery
- Poor recovery

Percentage of patients

- Aspirin
- Placebo
Role of aspirin in tuberculous meningitis: A randomized open label placebo controlled trial

U.K. Misra *, J. Kalita, P.P. Nair

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Hyponatremia in TBM (N=76)

- Occurred in 34(45%) pts
  - Mild (134-130 Meq/L) 3
  - Moderate (129-120 Meq/L) 32
  - Severe (<120 Meq/L) 8
- Related to
  - GCS, TBM severity
  - MV
  - Co-morbidity
- CSW related to severity of TBM 

(Misra et al J NS 2016)
### Cerebral salt wasting in TBM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSW (N34)</th>
<th>No CSW (N 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corona radiata inf</td>
<td>10 (67.5%)</td>
<td>3 (19%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>7 (9.4%)</td>
<td>10 (42%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Exudate</td>
<td>28 (82.4%)</td>
<td>26 (60.5%)</td>
<td>0.04</td>
</tr>
<tr>
<td>mRS &gt;2</td>
<td>21 (64%)</td>
<td>10 (26%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Infarction in TBM with CSW

- 15 y M TBM stage III
- Periventricular
- Int border zone infarct
- CSW Dx D1
Internal borderzone infarct in TBM with CSW

45 y M TBM stage III, DM2, Hypt CSW d 40, stroke 68
↓Na corrected after 12 d polyurea after 68 d
Conclusions

- Stroke in TBM is different
  - No TIA, RIND, more subtle
  - TB zone no stroke risk factor, Ischemic zone pts are older and have DM2, Hypt ↑ lipid
  - Mainly subcortical: tubercular / internal border zone
  - Asymptomatic 2/3, symptomatic 1/3
  - Occurs at any stage of TBM
  - Multi-factorial
Conclusions

- Cause of stroke
  - Vasculitis
  - Prothrombotic state
  - Hemodynamic factors, CSW / hypovolemic, hypotension hypo-perfusion
  - Co-morbidities

- Multipronged approach to stroke prevention in TBM
Possible mechanism of infarction in TBM

- Haemorrhhoelogy
- Change in micro vascular bed
- Response of vessels to neural or neurochemical factors
- Immunogenic phenomena Localize TB antigens in the vessel wall: endothelial, sub endothelial or smooth muscles

(Shankar et al 1989)