Pediatric TB Meningitis

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California Department of Public Health
Many Faces of TB
April 20th, 2016
Epidemiology

- Pediatric TB and TB meningitis (TBM) are “sentinel events” as markers of recent TB transmission

## Risk of TBM

<table>
<thead>
<tr>
<th>Age at Infection</th>
<th>Risk of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>Pulmonary disease 30-40%</td>
</tr>
<tr>
<td></td>
<td>TBM or miliary disease 10-20%</td>
</tr>
<tr>
<td>1-2 years</td>
<td>Pulmonary disease 10-20%</td>
</tr>
<tr>
<td></td>
<td>TBM or miliary disease 2-5%</td>
</tr>
<tr>
<td>2 years-adult</td>
<td>Pulmonary disease 5%</td>
</tr>
<tr>
<td></td>
<td>TBM or miliary disease 0.5%</td>
</tr>
</tbody>
</table>

The Epidemiology, Clinical Characteristics and Outcomes of Pediatric Central Nervous System TB in California from 1993-2011
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  Contra Costa County Health Department

• Pennan Barry, MD, MPH
  Chief Surveillance and Epidemiology Section
  California Department of Public Health
  Tuberculosis Control Branch
Objectives

1. Identify risk factors for pediatric CNS TB and death from TB

2. Determine how clinical and demographic factors impact outcome following CNS TB

3. Examine the effect of time to treatment on clinical outcome and stage at presentation
Pediatric CNS TB

- Rates of clinical morbidity (40-50%) and mortality (10-25%) in US pediatric series
  - Largest series are from resource limited settings but highly variable
- Poor outcomes associated with
  - Young age
  - Advanced clinical stage at presentation

vан Well G. et al. Twenty Years of Pediatric Tuberculous Meningitis: A retrospective cohort study in the Western Cape of South Africa. Pediatrics; 2009.
Pediatric CNS TB in California

Increase proportion of pediatric CNS disease in California in 2011

Prompted this large U.S. population based study of pediatric CNS TB
Risk Factors For CNS Tuberculosis

Registry Data

6,193 pediatric TB cases in California TB Registry 1993-2011

5,993 Cases of Non-CNS TB

200 Cases of CNS TB

TB registry data analysis

1) Identify demographic and clinical factors associated with pediatric CNS TB

2) Identify features associated with death from TB

## Demographics

<table>
<thead>
<tr>
<th>Demographic Factors</th>
<th>CNS TB n (%)</th>
<th>Non-CNS TB n (%)</th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0-4 y</td>
<td>144 (72)</td>
<td>2615 (44)</td>
<td>2.6 (1.6-4.2)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>150 (75)</td>
<td>3787 (63)</td>
<td>2.5 (1.0-6.3)</td>
</tr>
<tr>
<td>Hispanic U.S. birth</td>
<td>164 (82)</td>
<td>3482 (58)</td>
<td>1.9 (1.3-2.9)</td>
</tr>
</tbody>
</table>

^ 76% of US born children with CNS TB in 2010-2011 had at least one foreign born parent

## Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>CNS TB N (%)</th>
<th>Non-CNS TB N (%)</th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST Positive</td>
<td>105 (61)</td>
<td>5322 (93)</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>Culture Positive</td>
<td>118 (59)</td>
<td>1978 (33)</td>
<td></td>
</tr>
</tbody>
</table>

78% of cultures from CSF and 22% from non-CSF

### Factors Associated with Death

<table>
<thead>
<tr>
<th></th>
<th>Died (N = 32)</th>
<th>Survived (N = 6142)</th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS TB</td>
<td>9 (28)</td>
<td>191 (3)</td>
<td>3.8 (1.4-9.9)</td>
</tr>
<tr>
<td>Culture Positive</td>
<td>25 (78)</td>
<td>2056 (34)</td>
<td>6.2 (2.2-17.3)</td>
</tr>
</tbody>
</table>

### Factors Associated with Survival

<table>
<thead>
<tr>
<th></th>
<th>TST Positive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 (25)</td>
<td>5418 (88)</td>
</tr>
</tbody>
</table>

Age, gender, ethnicity, country of origin, susceptibilities and receipt of DOT were not associated with death

Summary

- Pediatric CNS TB cases were more likely <5 years, U.S.-born and Hispanic

- AFB culture positive and TST negative results were associated with both CNS TB and death

- CNS TB had a 4.5% vs. 0.4% mortality for non-CNS TB
Pediatric CNS TB Chart Review

- TB registry data lack information about:
  1. Clinical presentation
  2. Outcome
  3. Time to treatment

Chart Review

- 200 Cases of CNS TB
- 151 (76%) cases reviewed & 18 LHJ visited
- 92 (61%) with complete outcome information
- 79 (86%) cases with complete date information

Clinical Features
Outcome Analysis
Time to Treatment Analysis
CNS TB Clinical Features

0-4 yrs

5-18 yrs
Presenting symptoms by age

- Fever
- Vomiting
- AMS
- Seizure
- Cough
- Anorexia
- Focal deficit
- CN palsy
- Headache

0-4 yrs vs 5-18 yrs
Severity at Presentation

<table>
<thead>
<tr>
<th>MMRC</th>
<th>N (%)</th>
<th>Stage I</th>
<th>30 (26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>59 (51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>26 (23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MMRC = Modified Medical Research Council*
## CSF Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>(% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial LP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8</td>
<td>(6)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>125</td>
<td>(94)</td>
</tr>
<tr>
<td>CSF Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC ≥10 cells/µl</td>
<td>115</td>
<td>(92)</td>
</tr>
<tr>
<td>Lymphocytes &gt;50%</td>
<td>67</td>
<td>(63)</td>
</tr>
<tr>
<td>Glucose &lt;40 mg/dl</td>
<td>86</td>
<td>(66)</td>
</tr>
<tr>
<td>Protein &gt;100 mg/dl</td>
<td>85</td>
<td>(64)</td>
</tr>
</tbody>
</table>

Trend (p = 0.09) for normal CSF from an EVD vs LP

## Imaging Features

<table>
<thead>
<tr>
<th>Neuroimaging (MRI or CT scan)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>18 (14)</td>
</tr>
<tr>
<td><strong>Basilar enhancement</strong></td>
<td>75 (58)</td>
</tr>
<tr>
<td><strong>Hydrocephalus</strong></td>
<td>85 (66)</td>
</tr>
<tr>
<td><strong>Infarct</strong></td>
<td>50 (39)</td>
</tr>
<tr>
<td><strong>Focal lesion</strong></td>
<td>32 (25)</td>
</tr>
</tbody>
</table>

## Clinical Features

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS TB only</td>
<td>90 (69)</td>
</tr>
<tr>
<td>Disseminated</td>
<td>39 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Culture for Mtb</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>88 (58)</td>
</tr>
<tr>
<td>Negative</td>
<td>63 (41)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Susceptibility results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pansusceptible</td>
<td>69 (78)</td>
</tr>
<tr>
<td>INH resistance</td>
<td>4 (4)</td>
</tr>
<tr>
<td>MDR</td>
<td>3 (3)</td>
</tr>
<tr>
<td>PZA mono-resistance</td>
<td>10 (11)</td>
</tr>
</tbody>
</table>
# Treatment

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial TB regimen</strong></td>
<td></td>
</tr>
<tr>
<td>3 drugs (not EMB)</td>
<td>79 (56)</td>
</tr>
<tr>
<td>≥ 4 CNS drugs</td>
<td>62 (44)</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>106 (70)</td>
</tr>
<tr>
<td>No</td>
<td>45 (30)</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>EVD/VP shunt</td>
<td>70 (46)</td>
</tr>
<tr>
<td>Tuberculoma biopsy</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>
Predictors of good vs. poor outcome
Measuring post-treatment outcomes

• Six deficit areas assessed
  • Hearing, Vision, Language, Ambulation, Development, Focal neurologic deficits
  • Developed a standardized protocol for classifying deficits
  • Cases with information on ≥4 areas included for outcome analysis

• Determination of outcomes
  • **Good**: Normal (no deficits) or mild (1 area abnl) clinical sequelae
  • **Poor**: Moderate (2 areas abnl)/Severe clinical sequelae (3 areas abnl or complete deficit in 1) or death
Pediatric CNS TB Outcomes

Good outcome = 40%

- Normal: 20.7%
- Mild clinical sequelae: 19.6%

Poor outcome = 60%

- Moderate clinical sequelae: 13%
- Severe clinical sequelae: 33.7%
- Death: 13%

N = 92
Outcomes by Age

Aged 0–18mo, N = 42
- NL 2 (5%)
- Mild clinical sequelae 6 (15%)
- Moderate clinical sequelae 5 (12%)
- Severe clinical sequelae 21 (53%)
- Death 6 (15%)

Aged 18mo –4 yr, N = 31
- Normal 6 (19%)
- Mild clinical sequelae 7 (23%)
- Moderate clinical sequelae 4 (13%)
- Severe clinical sequelae 10 (32%)
- Death 4 (13%)

Aged 5–18y, N = 19
- Normal 11 (58%)
- Mild clinical sequelae 5 (26%)
- 5%
- Death 2 (11%)
## Clinical Severity Score

<table>
<thead>
<tr>
<th>Clinical Severity Score*</th>
<th>Good Outcome</th>
<th>Poor Outcome</th>
<th>Adjusted for Age PRR(^\wedge) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>13 (39)</td>
<td>2 (5)</td>
<td>Ref</td>
</tr>
<tr>
<td>Stage II</td>
<td>17 (52)</td>
<td>23 (52)</td>
<td>1.2 (0.99-1.5)</td>
</tr>
<tr>
<td>Stage III</td>
<td>3 (9)</td>
<td>19 (43)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
</tbody>
</table>

*MMRC = Modified Medical Research Council
\(^\wedge\)PRR = Prevalence Rate Ratio
Clinical Parameters

CSF Analysis
- Increased Protein
- *PRR 1.2 (1.03-1.4)

Neuroimaging
- Infarction
- *PRR 1.2 (1.04-1.3)

Multivariate

Clinical Severity
MMRC II or III
- PRR 1.2 (1.03 – 1.5)

Age
- PRR 1.4 (1.2 – 1.7)

*Age adjusted
No difference detected in good vs. poor outcome for:

- Clinical Symptoms
- *MTb* culture positive
- Susceptibilities
- Clinical case definition: definite vs. probable vs. possible
- Number of drugs in regimen
- Steroid use
- Duration of therapy
- Surgical treatment
Impact of time to treatment on outcome?

1. Date of TB treatment – Date of symptom onset
2. Date of TB Treatment – Date of 1st medical encounter
### Time to Treatment

<table>
<thead>
<tr>
<th></th>
<th>Good Outcome</th>
<th>Poor Outcome</th>
<th>Adjusted for Age PRR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Sx Onset–TB Rx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (days)</td>
<td>16</td>
<td>15</td>
<td>n/a</td>
</tr>
<tr>
<td>&lt; 10 days</td>
<td>8 (22)</td>
<td>8 (17)</td>
<td></td>
</tr>
<tr>
<td>≥ 10 days</td>
<td>28 (78)</td>
<td>39 (83)</td>
<td>1.04 (0.9-1.2)</td>
</tr>
<tr>
<td><strong>2. 1st Medical Encounter–TB Rx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (days)</td>
<td>11</td>
<td>11</td>
<td>n/a</td>
</tr>
<tr>
<td>&lt; 7 days</td>
<td>11 (31)</td>
<td>12 (27)</td>
<td></td>
</tr>
<tr>
<td>≥ 7 days</td>
<td>24 (69)</td>
<td>32 (73)</td>
<td>1.01 (0.9-1.2)</td>
</tr>
</tbody>
</table>

No association between time from symptom onset to presentation and the clinical stage at presentation
1. Early diagnosis remains critical for a good outcome
2. No clear linear relationship between time to treatment and outcome in this analysis
Source Case Identified
N = 58 (38%)

Contact Investigation 40%
Source Case Investigation 57%

61% Poor Outcome
Source case found in home 95%
76% Poor Outcome
Parent 52%
Relative 40%
Other 8%
Foreign Born 78%
Limitations

• No pre-existing validated outcome scale
• Limited access to pre-hospitalization records
• Difference in group that had outcomes available
• Small numbers limited:
  — Power to detect differences between outcome groups
  — Ability to adjust for confounding variables
Summary

• Almost 2/3 of pediatric CNS TB cases in California had poor clinical outcomes

• Age and severity of disease at presentation are associated with poor outcome but are not easily amenable to intervention

• Outcomes are better in Stage 1 disease but recognition of early non-specific CNS TB symptoms is challenging in young infants and with an increasingly rare disease
Clinical Interventions For CNS TB

• Think CNS TB for non-specific symptoms such as fever and vomiting in a young infant with TB exposure or who is high risk for exposure.

• Treat empirically based on imaging findings, CSF parameters and the absence of another etiology.

• Remember steroids for CNS TB treatment and that TST is only positive in about 50% of CNS TB cases.
Public health focus on TB prevention

• Prioritize *rapid* contact investigations involving children with appropriate treatment
• Emphasize LTBI risk assessment /testing/ treatment for adult caregivers (Cocooning)
• Emphasize routine TB risk assessments in infants (2 weeks, 6 mo, 1 yr, annually)
• Consider BCG in communities with high rates of recent TB transmission or for infants with extended travel to high TB incidence countries
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