Management of Cryptococcal Meningitis in HIV-infected children in National Pediatric Hospital

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Background and objectives

- Cryptococcal meningitis in HIV+ children
  - Less frequent than in adults (1% vs 5-8% in USA) (1,2)
  - Globally more frequent in Asia and Africa
  - Described in adults in Cambodia but never in children
  - Unpublished pediatric cases in Cambodia
- Between November 2005 and July 2006, 8 HIV+ children have received antifungal treatment for cryptococcal meningitis in National Pediatric Hospital (NPH).
- Retrospective study on medical files in order to improve diagnosis and treatment algorithm in NPH.

Methods

- Study population: 8 HIV infected children having received antifungal treatment for cryptococcal meningitis from November 2005 to July 2006.

- Medical records of these patients were available.

- We reviewed retrospectively clinical and laboratory findings, evolution and therapy regimen.
## Results

### Baseline characteristics of patients (n=8)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>7.7</td>
<td>(range 1.4 to 13.3)</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>Median Z score weight for height</td>
<td>-2 SD</td>
<td>(range -3 to -1SD)</td>
</tr>
<tr>
<td>Median CD4%</td>
<td>0.75%</td>
<td>(range 0.17 to 30%)</td>
</tr>
<tr>
<td>CD4%&lt;5</td>
<td>6</td>
<td>75%</td>
</tr>
<tr>
<td>Median Hemoglobin level g/dL (n=6)</td>
<td>9.0</td>
<td>(range 7.8 to 11.3)</td>
</tr>
<tr>
<td>Concomitant TB sputum smear +</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td>Concurrent TB treatment</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>HAART before crypto</td>
<td>4</td>
<td>50%</td>
</tr>
</tbody>
</table>
## Results

### Clinical findings

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>8</td>
<td>100%</td>
</tr>
<tr>
<td>Headaches</td>
<td>7</td>
<td>87.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>87.5%</td>
</tr>
<tr>
<td>Nuchal rigidity</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>Seizure</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td>Coma</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td>Elevated CSF pressure</td>
<td>4</td>
<td>100% (50%)</td>
</tr>
</tbody>
</table>

Declared duration of symptoms: 4 to 7 days
### Results
### Laboratory findings

<table>
<thead>
<tr>
<th>Findings</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryptococcal exams in CSF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indian Ink stain positive (n=8)</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>Mycological culture positive (n=6)</td>
<td>2</td>
<td>33.3% (25%)</td>
</tr>
<tr>
<td>Cryptococcal antigen positive (n=8)</td>
<td>8</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Standard CSF exams</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF white cells &gt;10/µL (n=8)</td>
<td>5</td>
<td>62.5%</td>
</tr>
<tr>
<td>WBC in CSF, median cells/µL (n=8)</td>
<td>40</td>
<td>(range, 4-310)</td>
</tr>
<tr>
<td>CSF proteins, median g/L (n=8)</td>
<td>0.32</td>
<td>(range, 0.12-1.3)</td>
</tr>
<tr>
<td>CSF glucose, median mmol/L (n=8)</td>
<td>2.8</td>
<td>(range, 0.7-4.2)</td>
</tr>
<tr>
<td>Cryptococcal antigen serum positive (n=1)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
# Laboratory findings
## Details per patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>Indian ink stain</th>
<th>Mycology culture (Sabouraud)</th>
<th>Crypto antigen CSF</th>
<th>Crypto antigen serum</th>
<th>CSF white cells</th>
<th>CSF proteins</th>
<th>CSF Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rare +</td>
<td>many colonies</td>
<td>+</td>
<td>NA</td>
<td>5</td>
<td>0,31</td>
<td>2,76</td>
</tr>
<tr>
<td>2</td>
<td>Negative</td>
<td>Sterile</td>
<td>+</td>
<td>NA</td>
<td>278 (91% ly)</td>
<td>1,3</td>
<td>2,9</td>
</tr>
<tr>
<td>3</td>
<td>Rare +</td>
<td>rare colonies</td>
<td>+</td>
<td>NA</td>
<td>70 (94% ly)</td>
<td>0,32</td>
<td>2,73</td>
</tr>
<tr>
<td>4</td>
<td>Negative</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>63 (70% ly)</td>
<td>1,25</td>
<td>0,65</td>
</tr>
<tr>
<td>5</td>
<td>Negative</td>
<td>Sterile</td>
<td>+</td>
<td>NA</td>
<td>4</td>
<td>0,22</td>
<td>4,2</td>
</tr>
<tr>
<td>6</td>
<td>Rare +</td>
<td>Sterile</td>
<td>+</td>
<td>NA</td>
<td>16 (96% ly)</td>
<td>0,12</td>
<td>3,23</td>
</tr>
<tr>
<td>7</td>
<td>Negative</td>
<td>Sterile</td>
<td>+</td>
<td>Negative</td>
<td>8</td>
<td>0,14</td>
<td>2,77</td>
</tr>
<tr>
<td>8</td>
<td>Rare +</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>310 (96%)</td>
<td>0,46</td>
<td>2,31</td>
</tr>
</tbody>
</table>
Treatment (1)
Antifungal treatments

Induction
- All patients received amphotericin B IV treatment
  - Mean dose: 1 mg/kg/day (range, 0.7-1.2 mg/kg/day)
  - Median duration of treatment: 16 days (range, 10-21 days)
  - Adverse events
    - Fever during perfusion noted for one patient
    - No allergic reactions noted
    - Fall of hemoglobin (-27%) in 1 patient
    - No monitoring of creatinine realized

Consolidation and maintenance
- Fluconazole
  - Consolidation treatment: 6 patients mean dose used 11.3 mg/kg/day in 2 doses, at least 8 weeks
  - One patient was started directly on secondary prophylaxis fluconazole treatment and one patient delayed on 2ndary proph.
Treatment (2)
Management of elevated intracranial pressure

CSF opening pressure measured in 4:
- Elevated (>200 mm H₂O) in 4
- Range from 250 to 800 mm H₂O

CSF pressure noted as “high” without measure: 2

- Patients with elevated intracranial pressure (ICP) had lumbar puncture for evacuation of CSF
  - 6 patients had lumbar puncture for evacuation of CSF
  - Median number of LP for drainage: 1.5 (range 1 to 7)
  - 10 to 23 ml evacuated each time
  - Repetition of LP based on clinical symptoms and previous measure

- No CT scan was performed prior to LP
Measure of CSF opening pressure
Results
Patients on HAART before crypto

4 patients on HAART before cryptococcosis

- ART regimen: D4T 3TC NVP
- Delay between ART and crypto:
  - Median 61 days
  - 3 patients with ART less than 10 weeks
    - M6 CD4% improved median 11.3% (11.2-14%)
    - VL M6 available in 2 undetectable
  - 1 patient ARV experienced since 3 years
    - CD4%: 3.3 %, VL: 5.4 Log
    - Diagnosis of HAART failure and switch to 2nd line
Results

Early evolution

- Clinical evolution successful in 6 with apyrexia and diminution of headaches
- LP control at day 14 performed in 3, positive for 1 on Indian Ink stain
- Early relapse in one patient
  - Persistence of headaches, elevated IPC, LP + (Indian Ink+) on fluconazole maintenance treatment
  - Successful evolution under new treatment by amphotericin B
- One presented secondary neurological sequelae
- Length of hospital stay:
  - median 44 days
  - Prolonged because of associated pathologies (TB, malnutrition)
Results
Long term outcome

- All patients are alive today and treated on HAART
- One presented secondary neurological sequelae consisting of hydrocephaly (confirmed by CT scan)
- One late relapse of cryptococcal meningitis
  - After 6 Mo of ART and 7 Mo of fluconazole prophylaxis
  - Headaches, fever
  - CSF opening pressure: 350 mm H$_2$O
  - Ag crypto CSF +, Ag crypto serum +,
  - Indian ink stain +, culture neg
Discussion (1)

Diagnosis

- In 4 patients cryptococcosis diagnosis is based only on positive antigen in CSF
  - Diagnosis value of CSF cryptococcal antigen alone.
  - Gold standard for cryptococcosis diagnosis = culture
  - But CSF cryptococcal antigen used alone as diagnosis criteria by some authors \(^{(20)}\)
  - High sensitivity (94.1\%) \(^{(46)}\)
    - Dilution not performed so titer of crypto antigens is not available
    - Remains in CSF for long periods (23 weeks) \(^{(23)}\)
    - Not to be used alone in relapse diagnosis

Discussion (2)
Diagnosis

- **Serum CSF antigen**
  - Thailand sensibility 91.4% in adults specificity 83.3% good and simple screening method (15)
  - Serum CSF antigen + in 99% of cases of crypto meningitis (18)
  - Patient #7: possible false positive as antigen in CSF + alone and antigen in serum negative?

- **Frequency of + India ink stain (50%) is less than in Thai series of children (94%)** (2)

- **Compared to adult cases, WBC in CSF is high**
  - Median 0 cells (range, 0-5 cells/μL) in adult series (35)

Discussion (3)
On ART: IRIS, symptomatic relapse?

- Immune Reconstitution Inflammatory Syndrome IRIS
cryptococcal meningitis has been described \(^{(19,11)}\)
  - Mechanism: inflammatory syndrome due to persistence of
    cryptococcal antigens in CSF
  - Treatment by steroids
- Symptomatic relapse can also occur on fluconazole
  prophylaxis and ARV treatment \(^{(19)}\)
  - Associated to fluconazole resistance
- In our 4 cases, new infections with no prior
  cryptococcosis infections: latent cryptococcosis revealed
  by ART.
- One late relapse on ARV and fluconazole prophylaxis for
  6 Mo

Discussion (4)
Treatment regimen

- **Induction therapy**
  - Amphotericin B
    - Recommended with flucytosine (not available in NPH) \(^\text{(18)}\)
    - Alone acceptable alternative \(^\text{(18, 37, 47)}\)
    - Dose recommended 0.7 to 1 mg/kg/day
    - Pre-medication paracetamol, steroids, anti-H\(_1\) drugs, hyper-hydratation
  - Fluconazole alone used but not recommended on 1\(^{st}\) intention \(^\text{(18)}\)

- **Consolidation therapy** \(^\text{(18, 47)}\)
  - Fluconazole (5-6 mg/kg BID), 8 weeks

- **Maintenance therapy (secondary prophylaxis)** \(^\text{(18, 47)}\)
  - Fluconazole low dose (3-6 mg/kg OD)
  - No data on safety of discontinuation of fluconazole in children \(^\text{(47)}\)
  - Start ART also recommended as maintenance therapy \(^\text{(18)}\)

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Discussion (5)
Primary fluconazole prophylaxis

- Recommended in national guidelines
  - Fluconazole used for primary and secondary prophylaxis
  - Formerly not implemented in NPH as cryptococcal meningitis was uncommon in children in the 1st year of follow up
- Now implemented in NPH for children with CD4<5%
- Increasing in vitro resistance to fluconazole described in Cambodia, potentially due to secondary prophylaxis (44)
- Pharmacokinetic of fluconazole:
  - Concomitant use of rifampicin reduces area under the Fluconazole concentration-time curve by effect on cy P450 (20)
  - Fluconazole should be taken at night when taken with rifampicin

Discussion (6)
Management of elevated intracranial pressure

- Elevated ICP defined as CSF opening pressure > 200 mmH₂O in lateral decubitus
- Associated with high mortality in adults
- Due to mechanical obstruction by cryptococci or capsular polysaccharides blocking passage of CSF across arachnoid villi
  - ≠ obstructive hydrocephalus (no risk of cerebral herniation w/ LP)
- Management:
  - Repeated LP for drainage and treatment of high ICP\(^{35,18}\)
  - Acetazolamide, mannitol and steroids not recommended
  - Possible lumbar or ventricular drain if iterative LP not efficient\(^{18}\)

**Discussion (7)**

**Drainage LP protocol for elevated ICP**

<table>
<thead>
<tr>
<th>ICP (CSF opening pressure)</th>
<th>Volume to drain</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200 mm H$_2$O</td>
<td>10 to 15 ml</td>
<td>If clinical symptoms of elevated ICP</td>
</tr>
<tr>
<td>200 to 350 mm H$_2$O</td>
<td>10 to 15 ml</td>
<td>Twice a week</td>
</tr>
<tr>
<td>&gt; 350 mm H$_2$O</td>
<td>10 to 15 ml</td>
<td>Daily until ICP &lt; 200 mm H$_2$O or &lt; 50% of initial value</td>
</tr>
</tbody>
</table>

- In case of very high ICP, it is recommended to measure the CSF pressure after drainage
- Possible lumbar or ventricular drain (ventriculoperitoneal shunt) if failure of iterative LP
Conclusion

- Cryptococcal meningitis is not uncommon in HIV+ children cohort in NPH specially with severe immunodepression.
- Fluconazole prophylaxis is now started in all HIV infected children followed in NPH specific HIV clinic with CD4 5% or less
- Clear treatment algorithm has been set up in NPH including management of elevated ICP.
- CSF opening pressure should be measured when performing lumbar puncture for HIV infected children.
Acknowledgements

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