Title: Absence of Cerebrospinal Fluid Pleocytosis in Tuberculous Meningitis is a Common Occurrence in HIV Co-infection and a Predictor of Poor Outcomes

Author: Fiona V. Cresswell

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144
To appear in: International Journal of Infectious Diseases

Author: Ananta S. Bangdiwala

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144
To appear in: International Journal of Infectious Diseases

Author: David B. Meya

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144
To appear in: International Journal of Infectious Diseases

Author: Nathan C. Bahr

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144
To appear in: International Journal of Infectious Diseases

Author: Jose E. Vidal

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144
To appear in: *International Journal of Infectious Diseases*

Author: M. Estée Török

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144

To appear in: *International Journal of Infectious Diseases*

Author: Le Thi Phuong Thao

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144

To appear in: *International Journal of Infectious Diseases*

Author: Guy E. Thwaites

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144

To appear in: *International Journal of Infectious Diseases*

Author: David R. Boulware

PII: S1201-9712(18)30015-8
DOI: https://doi.org/10.1016/j.ijid.2018.01.014
Reference: IJID 3144

To appear in: *International Journal of Infectious Diseases*

Received date: 15-11-2017

Please cite this article as: Boulware David R. Absence of Cerebrospinal Fluid Pleocytosis in Tuberculous Meningitis is a Common Occurrence in HIV Co-infection and a Predictor of Poor Outcomes.*International Journal of Infectious Diseases* https://doi.org/10.1016/j.ijid.2018.01.014
Absence of Cerebrospinal Fluid Pleocytosis in Tuberculous Meningitis is a Common Occurrence in HIV Co-infection and a Predictor of Poor Outcomes

Fiona V Cresswell¹,²
Ananta S Bangdiwala³
David B Meya²,⁴
Nathan C Bahr⁵
Jose E Vidal⁶,⁷
M. Estée Török⁸
Le Thi Phuong Thao⁹
Guy E Thwaites⁹,¹⁰
David R Boulware³

¹ Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK
² Infectious Diseases Institute, Kampala, Uganda
³ Department of Medicine, University of Minnesota, Minneapolis, MN, USA
⁴ College of Health Sciences, Makerere University, Kampala, Uganda
⁵ Division of Infectious Diseases, Department of Medicine, University of Kansas, Kansas City, KS, USA
⁶ Department of Neurology, Instituto de Infectologia Emílio Ribas, São Paulo, Brazil
⁷ Laboratório de Investigação Médica 49, Instituto de Medicina Tropical, Universidade de São Paulo, São Paulo, Brazil
⁸ Department of Medicine, University of Cambridge, Cambridge, United Kingdom
⁹ Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam
¹⁰ Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, UK

Corresponding Author

Fiona V Cresswell, Infectious Diseases Institute, Kampala, P.O. Box 22418. Uganda. fionacresswell@doctors.org.uk

Keywords: TB meningitis, TBM, HIV, CSF pleocytosis, acellular, outcomes

Main Text:

We read with interest the article by Erdem et al. reporting absence of cerebrospinal fluid (CSF) pleocytosis (≤5 cells/µl) in 3% (19/507) of HIV-negative tuberculous meningitis (TBM) patients (Erdem et al., 2017).
We wish to highlight both the significance and higher incidence of acellular CSF among HIV-infected adults with TBM. In reviewing 85 microbiologically-confirmed, HIV-associated TBM cases in Uganda, 33% (28/85) had acellular CSF. Acellular CSF was also commonly reported among other HIV-infected microbiologically-confirmed TBM cohorts: 26% (5/19) in Zimbabwe, 19% (20/108) in Brazil, and 21% (18/91) in Argentina (Table 1) (Cecchini et al., 2007, Croda et al., 2010, Hakim et al., 2000, Vidal et al., 2010). Prevalence of acellular CSF correlated with the severity of immunosuppression in the Argentinian cohort and occurred twice as often in CD4 counts <50 cells/μl (33%, 9/28) than with >50 cells/μl (15%, 5/31) (Cecchini et al., 2009). In Vietnam, acellular CSF is less common (4%, 20/461) despite advanced immunosuppression (median CD4 39 cells/μl). Variation between cohorts may be attributable to variable time to CSF analysis, M. tuberculosis strain type, or genetic differences in host immune responses between geographically distinct cohorts (Caws et al., 2008).

In cryptococcal meningitis, both acellular CSF and elevated CSF neutrophil counts have been associated with poorer outcomes (Scriven et al., 2015). Recently, the observation of a paucity of inflammation or inappropriate neutrophil-mediated inflammation adversely impacting survival has also been confirmed in TBM. Thao et al. demonstrated that in Vietnamese adults lower CSF lymphocyte count was an independent predictor of mortality, regardless of HIV-status (Thao et al., 2017) and van Laarhoven et al. found that high CSF neutrophils were associated with death in a large Indonesian, predominantly HIV-negative, cohort (van Laarhoven et al., 2017).

In HIV-infection, the degree of immunosuppression affects the intracerebral inflammatory phenotype. Those with CD4+ T-cell count <150 cells/μl had a higher median CSF neutrophil percentage than those with CD4+ count >150 cells/μl (25% versus 10%, P=0.021) and this correlated with higher CSF cytokine concentrations (Thuong et al., 2017). Both increased CSF neutrophils and raised inflammatory mediator concentrations predispose to clinical deterioration after starting HIV therapy, resulting in higher morbidity and mortality (Marais S et al., CID 2014). This inflammation may contribute to the 44% mortality reported by Thuong in those with <150 CD4 cells/μl compared with 13% mortality in >150 CD4 cells/μl. Improved understanding of the drivers and consequences of the inflammatory phenotype in HIV-associated TBM may enable optimised use of adjunctive corticosteroids or host-directed therapy.

“Typical” CSF findings (cells >5/μl, protein >45g/l, glucose <45mg/dl) occur in under two-thirds of HIV-infected TBM patients, so clinical acumen and highly sensitive diagnostic tests are critical (Croda et al., 2010). The new Xpert MTB/Rif ‘Ultra’ assay has greater analytical sensitivity and may reduce diagnostic dilemma in HIV-associated TBM (Bahr et al., 2018). These data should reinforce that acellular CSF is a poor prognostic sign and is relatively common among HIV-infected persons, 12%
(91/776) among the cohorts summarized. High clinical index of suspicion remains vital for timely, often empiric TBM therapy to reduce death and disability.

**Acknowledgements:** FVC is supported by Wellcome Trust, UK (ITCRZL80). ASB, DBM, and DRB are supported by Fogarty International Center and National Institute of Neurologic Diseases and Stroke (R01NS086312). MET is supported by the Academy of Medical Sciences, the Health Foundation and the NIHR Cambridge Biomedical Research Centre. GT and LTPT were supported by the Wellcome Trust, UK.

**Conflicts of Interests:** No conflicts of interest are declared.
References


### Table 1. Summary HIV-infected cohorts with microbiologically confirmed tuberculous meningitis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Uganda (Hakim et al.)</th>
<th>Zimbabwe (Croda et al.)</th>
<th>Brazil (Cecchini et al.)</th>
<th>Argentina (Thao et al.)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>85</td>
<td>21</td>
<td>108</td>
<td>101</td>
</tr>
<tr>
<td>Median CD4 cells/µl</td>
<td>81</td>
<td>131</td>
<td>65</td>
<td>53</td>
</tr>
<tr>
<td>CSF lymphocytes /mm³</td>
<td>75 (0-2450)</td>
<td>N/A</td>
<td>49 (0-100)</td>
<td>N/A</td>
</tr>
<tr>
<td>Acellular CSF ≤5 cells/µl</td>
<td>28 (33%)</td>
<td>5 (26%)b</td>
<td>20 (19%)</td>
<td>18 (21%)c</td>
</tr>
<tr>
<td>Normal CSF (white cells, protein and glucose)a</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
<td>4 (4%)</td>
<td>N/A</td>
</tr>
<tr>
<td>In hospital Mortality</td>
<td>54%e</td>
<td>67%</td>
<td>29%</td>
<td>63%</td>
</tr>
<tr>
<td>9-month Mortality</td>
<td>N/A</td>
<td>N/A</td>
<td>41%</td>
<td>N/A</td>
</tr>
<tr>
<td>Mortality in patients with acellular CSF</td>
<td>39%</td>
<td>N/A</td>
<td>55%</td>
<td>N/A</td>
</tr>
<tr>
<td>Mortality in patients with normal CSF</td>
<td>0%</td>
<td>N/A</td>
<td>75%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Values represent N (%) or median (range).

* microbiologically confirmed HIV-associated TBM cases from Thao et al. Vietnam cohort included

N/A is not data available

a “Normal CSF” defined as white cells ≤5/mm³, protein <45g/l, glucose >45mg/dl (2.5mmol/l).  
b CSF data available for n=19.  
c CSF data available for n=91.  
d CSF data available for 458.  
e outcome known for n=69.