

Accepted Manuscript

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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

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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>

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

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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/ μ l) 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 (**Table1**)(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/ μ l (33%, 9/28) than with >50 cells/ μ l (15%, 5/31) (Cecchini et al., 2009). In Vietnam, acellular CSF is less common (4%, 20/461) despite advanced immunosuppression (median CD4 39 cells/ μ l). 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/ μ l had a higher median CSF neutrophil percentage than those with CD4⁺ count >150 cells/ μ l (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/ μ l compared with 13% mortality in >150 CD4 cells/ μ l. 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 $>5/\mu$ l, protein >45 g/l, glucose <45 mg/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.

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Cohort	Uganda	Zimbabwe (<i>Hakim et al.</i>)	Brazil (<i>Croda et al.</i>)	Argentina (<i>Cecchini et al.</i>)	Vietnam (<i>Thao et al.</i>)*
Study Period	2011 - 2017	1994	1999-2007	1996-2004	2004-2015
N	85	21	108	101	461
Median CD4 cells/ μ l	81	131	65	53	39
CSF lymphocytes /mm ³	75 (0-2450)	N/A	49 (0-100)	N/A	103 (0-6004)
Acellular CSF with ≤ 5 cells/ μ l	28 (33%)	5 (26%) ^b	20 (19%)	18 (21%) ^c	20 (4%) ^d
Normal CSF (white cells, protein and glucose) ^a	3 (4%)	0 (0%)	4 (4%)	N/A	2 (0.4%)
In hospital Mortality	54% ^e	67%	29%	63%	N/A
9-month Mortality	N/A	N/A	41%	N/A	51%
Mortality in patients with acellular CSF	39%	N/A	55%	N/A	60%
Mortality in patients with normal CSF	0%	N/A	75%	N/A	100%

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

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 $\leq 5/\text{mm}^3$, protein $< 45\text{g/l}$, glucose $> 45\text{mg/dl}$ (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.