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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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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.

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References

- Bahr NC, Nuwagira E, Evans EE, Cresswell FV, Bystrom PV, Byamukama A, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. *Lancet Infect Dis* 2018;18(1):68-75.
- Cecchini D, Ambrosioni J, Brezzo C, Corti M, Rybko A, Perez M, et al. Tuberculous meningitis in HIV-infected patients: drug susceptibility and clinical outcome. *AIDS* 2007;21(3):373-4.
- Cecchini D, Ambrosioni J, Brezzo C, Corti M, Rybko A, Perez M, et al. Tuberculous meningitis in HIV-infected and non-infected patients: comparison of cerebrospinal fluid findings. *Int J Tuberc Lung Dis* 2009;13(2):269-71.
- Croda MG, Vidal JE, Hernandez AV, Dal Molin T, Gualberto FA, de Oliveira AC. Tuberculous meningitis in HIV-infected patients in Brazil: clinical and laboratory characteristics and factors associated with mortality. *Int J Infect Dis* 2010;14(7):e586-91.
- Erdem H, Ozturk-Engin D, Cag Y, Senbayrak S, Inan A, Kazak E, et al. Central Nervous System Infections in the Absence of Cerebrospinal Fluid Pleocytosis. *Int J Infect Dis* 2017.
- Hakim JG, Gangaidzo IT, Heyderman RS, Mielke J, Mushangi E, Taziwa A, et al. Impact of HIV infection on meningitis in Harare, Zimbabwe: a prospective study of 406 predominantly adult patients. *AIDS* 2000;14(10):1401-7.
- Marais S, Wilkinson KA, Lesosky M, Couseens AK, Deffur A, Pepper DJ et al. Neutrophil-associated central nervous system inflammation in tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis*. 2014;59(11):1638-47
- Scriven JE, Rhein J, Hullsiek KH, von Hohenberg M, Linder G, Rolfes MA, et al. Early ART After Cryptococcal Meningitis Is Associated With Cerebrospinal Fluid Pleocytosis and Macrophage Activation in a Multisite Randomized Trial. *J Infect Dis* 2015;212(5):769-78.
- Thao LTP, Heemskerk AD, Geskus RB, Mai NTH, Ha DTM, Chau TTH, et al. Prognostic models for 9 month mortality in tuberculous meningitis. *Clin Infect Dis* 2017:*In Press*.
- Thuong NTT, Heemskerk D, Tram TTB, Thao LTP, Ramakrishnan L, Ha VTN, et al. Leukotriene A4 Hydrolase Genotype and HIV Infection Influence Intracerebral Inflammation and Survival From Tuberculous Meningitis. *J Infect Dis* 2017;215(7):1020-8.
- van Laarhoven A, Dian S, Ruesen C, Hayati E, Damen M, Annisa J, et al. Clinical parameters, routine inflammatory markers, and LTA4H genotype as predictors of mortality among 608 patients with tuberculous meningitis in Indonesia. *J Infect Dis* 2017;215(7):1029-39.
- Vidal JE, de Oliveira AC, Hernandez AV. CD4+ T-cell count and cerebrospinal fluid findings in HIV-infected patients with tuberculous meningitis. *Int J Tuberc Lung Dis* 2010;14(11):1496-7; author reply 7.

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.