Cerebrospinal Fluid Protein Clinical Impact In HIV-Associated Cryptococcal Meningitis

John Kasibante[1], Eesha Irfanullah[2], Abduljaweed Wele[2], Kenneth Ssebambulidde[1], Samuel Okurut[1], Enock Kagimu[1], Jane Gakuru[1], Morris K. Rutakingirwa[1], Timothy Mugabi[1], Edwin Nuwagira[3], Samuel Jjunju[1], Lillian Tugume[1], Laura Nsangi[1], Abdu K Musibire[1], Conrad Muzoora[3], David B. Meya[1,2], David R. Boulware[2], **Mahsa Abassi[2]**
[1]Infectious Diseases Institute-Makerere University, Kampala, Uganda. [2]University of Minnesota, Minneapolis, USA. [3]Mbarara University of Science and Technology, Mbarara, Uganda.

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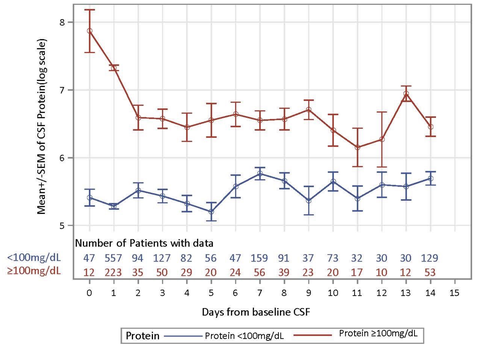
BACKGROUND

In HIV-associated cryptococcal meningitis, cerebral spinal fluid (CSF) protein levels are highly variable. However, the association between CSF protein and clinical outcomes are not well understood. We sought to understand the relationship between CSF protein levels and clinical presentation and treatment outcomes in cryptococcal meningitis among adults living with HIV. Additionally, we assessed the relationship between CSF protein levels and factors influencing cryptococcal meningitis outcomes, including seizures, altered level of consciousness, $CD4^+$ T-cell count, CSF fungal burden, CSF opening pressure, and cytokine profile. Gaining insights into the role of CSF protein in cryptococcal meningitis may help to establish its clinical utility as a prognostic biomarker in disease outcomes.

METHODS

This study combined 874 Ugandan adults with HIV-associated cryptococcal meningitis from two clinical trials: (i) the Adjunctive Sertraline for the Treatment of HIV-associated Cryptococcal Meningitis (ASTRO-cm) from March 9, 2015 to May 29, 2017; and (ii) the AMBIsome Therapy Induction Optimisation (AMBITION-cm) from January 2018 through February 2021. CSF protein levels were measured at baseline and throughout hospitalization **(Figure 1).** CSF cytokines and chemokines were measured at baseline. We summarized demographic and laboratory variables by baseline CSF protein level <100 mg/d vs. ≥100 mg/dL.

Figure 1: Longitudinal Mean CSF Protein (mg/dL) levels



In HIV-associated cryptococcal meningitis, baseline CSF protein ≥100 mg/dL, is associated with a more pronounced CSF inflammatory response as compared to CSF protein <100 mg/dL.

RESULTS

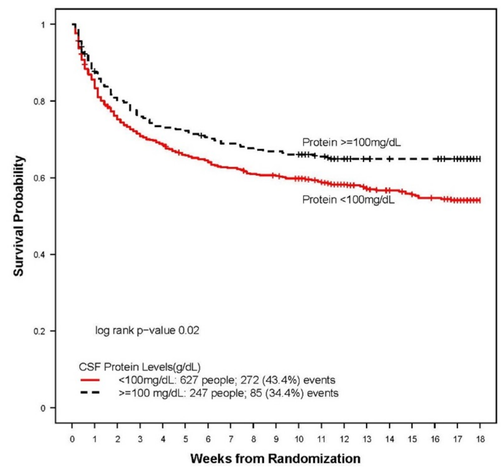
- Baseline CSF protein ≥100 mg/dL was associated with a Glasgow coma scale (GCS) score <15 (p<0.01) and self-reported seizures (p=0.03) **(Table 1)**.
- CSF protein ≥100 mg/dL was associated with a higher baseline CD4 cell count (p<0.001), higher CSF white cell count (p<0.001), lower CSF cryptococcal fungal burden (p<0.001), and a higher percentage of sterile CSF cultures at day 14 (p=0.02) **(Table 1)**.
- Baseline CSF protein ≥100 mg/dL was associated with higher measurements of CSF cytokines IL1B, IL1Ra, IL6, CXCL8/IL8, IL-17, granzyme B, CXCL1/GROA, and PDL1 (p<0.05).
- There was no significant difference in 18-week mortality between CSF protein <100 mg/dL as compared to CSF protein ≥100 mg/dL **(Figure 2)**.

Table 1: Clinical presentation and outcomes by Baseline CSF protein levels

	CSF protein <100mg/dL		CSF protein ≥100mg/dL		P-value[1]
	N	Median [IQR] or N (%)	N	Median [IQR] or N (%)	
Age (years)	627	35 [30, 40.0]	247	35 [30, 42.0]	0.55
Female	627	256 (40.8)	247	87 (35.2)	0.14
Weight (kg)	547	51 [46, 60.0]	222	53 [47, 60.0]	0.33
Currently on ART	626	300 (47.9)	247	117 (47.4)	0.94
Seizures; N (%)	627	89 (14.2)	247	51 (20.6)	0.02
GCS < 15	626	224 (35.8)	247	113 (45.7)	<0.01
CD4 cells/mL	600	15 [6, 41.0]	238	28 [10, 65.0]	<0.001
CSF Culture, *Cryptococcus* CFUs/mL	620	47863 [1585, 316228]	246	12882 [200, 199526]	<0.001
CSF White cells/mL	622	4 [4, 10]	244	55 [4, 150]	<0.001
Day 14 Sterile CSF Culture	429	191 (44.5)	149	83 (55.7)	0.02

Data are median (P25, P75) or N (%). [1]Kruskal-Wallis test for medians; Fisher Exact tests for proportions

Figure 2: 18 Week Survival by Baseline CSF Protein



CONCLUSIONS

Baseline CSF protein levels influence clinical presentation in cryptococcal meningitis. Individuals with CSF protein ≥100 mg/dL demonstrate a robust immune response against cryptococcal disease as evidenced by a lower CSF fungal burden at baseline, a greater percentage of sterile CSF cultures at day 14 and improved 18-week mortality. Individuals with CSF protein ≥100 mg/dL who present with altered mental status and/or seizures at baseline may be experiencing a host-damage response that may account for similar 2-week mortality rates to those who present with a deficient or absent cell-mediated immune response. Further studies are warranted to determine if CSF protein levels can be used as a rapid diagnostic tool to target individuals who would benefit from targeted immunomodulatory therapy to dampen an exaggerated immune response.

ADDITIONAL KEY INFORMATION

Author Contact Information: Dr. John Kasibante. Email: johnkasi93@gmail.com

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