Risk Factors Associated With Neurocognitive Impairment In Cryptococcal Meningitis

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Laura Nsangi[1], Biyue Dai[3], Kenneth Ssebambulidde[1], Lillian Tugume[1], Edwin Nuwagira[2], Darlisha A Williams[3], Abdu Musubire[1], David R Boulware[3], David B Meya[1,3], Mahsa Abassi[3]

[1]Infectious Diseases Institute-Makerere University, Kampala, Uganda, [2]Mbarara University of Science and Technology, Mbarara, Uganda, [2]University of Minnesota, Minneapolis, Minnesota, USA

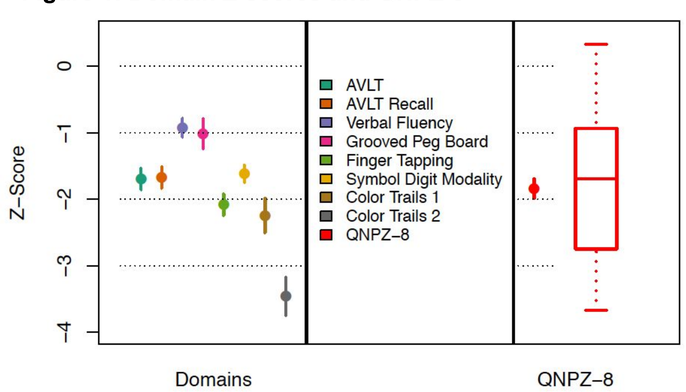
BACKGROUND

The magnitude and clinical risk factors of sustained neurocognitive impairment in HIV-associated cryptococcal meningitis are not well described. We sought to understand the magnitude and clinical risk factors associated with neurocognitive impairment among cryptococcal meningitis survivors.

METHODS

We performed neuropsychological testing on 210 participants with first episode cryptococcal meningitis enrolled into the the Adjunctive Sertraline for the Treatment of HIV-associated Cryptococcal Meningitis (ASTRO-cm) trial from March 9, 2015 to May 29, 2017. Neurocognitive assessment (NCA) was performed at week 12 (+/- 3) and consisted of a battery of tests evaluating 8 neurophysiological domains. A composite quantitative neurocognitive performance z-score (QNPZ) was calculated as the mean of eight individual z-scores and standardized to an HIV-negative Ugandan cohort **(Figure 1)**. An incomplete test, due to study participant illness, was assigned a score of 2 SD below the mean for the domain tested. Neurocognitive impairment (NCI) is defined as a QNPZ8 z-score <-1. We compared demographic variables and clinical characteristics by QNPZ-8 groups; QNPZ-8 <-1 vs. QNPZ-8 ≥ -1).

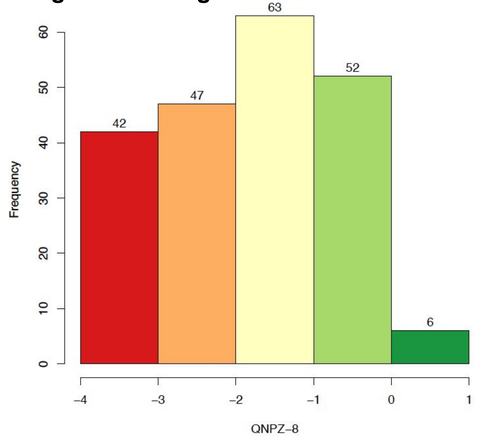
Figure 1: Domain Z-scores and QNPZ-8



Neurocognitive impairment among cryptococcal meningitis survivors is common and associated with baseline seizures, altered mental status, and low serum sodium.

RESULTS

Figure 2: Histogram of QNPZ-8 Scores



- 72% (152/210) of study participants demonstrated neurocognitive impairment (QNPZ-8<-1) at 12-weeks post cryptococcal meningitis diagnosis **(Figure 2)**.
- Among cryptococcal meningitis survivors, 12-week neurocognitive impairment (QNPZ-8<-1) was associated with a baseline GCS<15, self-reported seizures, and lower serum sodium levels **(Table 1)**.
- Among cryptococcal meningitis survivors, 12-week neurocognitive impairment was not associated with baseline CD4+ T cell count, intracranial opening pressures, or CSF cryptococcal fungal burden **(Table 1)**.

Table 1: Demographic and Clinical Characteristics by QNPZ-8 Score

	N	QNPZ-8 < -1	N	QNPZ8 >= -1	p-value[1]
Age	152	35 [30, 40]	58	32 [27, 38]	0.09
Male	152	97 (63.8%)	58	38 (65.5%)	0.82
Currently on ART	152	73 (48.0%)	58	29 (50.0%)	0.80
CD4+ cell count/∝L	152	21 [8, 57]	58	13 [6, 53]	0.36
Glasgow Coma Score <15	152	66 (56.6%)	58	12 (79.3%)	**<0.01**
Seizures	152	24 (15.8%)	58	3 (5.2%)	**0.04**
Serum Sodium, mmol/L	152	129 [126, 133]	58	132 [128, 134]	**0.03**
CSF Opening pressure, cmH_2O	152	26 [20, 38]	58	27 [20, 35]	0.84
CSF *Cryptococcus* log_{10}CFU/mL	152	4.51 [2.78, 5.32]	58	4.11 [2.59, 4.85]	0.13

[1]Kruskall-Wallis test for medians; Chi-square test for proportions
Data presented as either N (%) or Median [IQR]

Table 2: CSF Sterility and WBC by QNPZ=8 Score

	N	QNPZ-8 < -1	N	QNPZ8 >= -1	p-value[1]
Day 0 – Sterile CSF	151	8 (5.3%)	58	8 (13.8%)	**0.04**
Day 0 – CSF WBC	149	<5 [<5, 100]	57	<5 [<5, 45]	0.09
Day 7 – Sterile CSF	152	41 (27.0%)	58	20 (34.5%)	0.28
Day 7 – CSF WBC	34	<5 [<5, 8]	14	25 [<5, 100]	**0.03**
Day 14 – Sterile CSF	152	87 (57.2%)	58	36 (62.1%)	0.53
Day 14 – CSF WBC	47	<5 [<5, 45]	16	5 [<5, 19]	0.86

Data presented as either N (%) or Median [IQR]
[1]Kruskall-Wallis test for medians; Chi-square test for proportions
[2]Units White blood cells (cells/∝L)

- Persons with baseline sterile CSF culture were more likely to be non-impaired at week 12 **(Table 2).**
- While there were no observed differences between baseline CSF WBCs between groups, non-impaired subjects had higher median CSF WBC on day 7 as compared to the impaired group **(Table 2)**.

CONCLUSIONS

Neurocognitive impairment at week 12 is common among cryptococcal meningitis survivors. Baseline GCS<15, seizures, and low serum sodium are risk factors for sustained neurocognitive impairment. Baseline sterile CSF cryptococcal cultures and early rise in CSF WBC is associated with improved neurocognitive performance at week 12. Future analysis are needed to model risk factors for sustained neurocognitive impairment. Future studies looking into the impact and degree of immune recovery during cryptococcal meningitis induction therapy to improve neurocognitive outcomes are warranted.

LIMITATIONS

Baseline NCA are not performed because of disease severity. QNPZ-8 scores can be impacted by missing imputation when a study participant is unable to complete a test.

ADDITIONAL KEY INFORMATION

Author Contact Information: Laura Nsangi MBChB
Email: jlaura88800@gmail.com

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