Abstract 746

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CSF IMMUNE RESPONSES ASSOCIATED WITH DEPRESSION FOLLOWING CRYPTOCOCCAL MENINGITIS

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for the Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis (ASTRO-CM) Trial Team.

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Introduction

- Depression is common in people with serious illness such as following meningitis and those with advanced HIV.
- There is known to be an association with immunologic factors and depression, however most studies have used cytokines from the blood and not CSF.
- We evaluated a number of factors, mostly from the CSF, to see if there is a difference in those who get depressed and those who do not.

Methods

•Participants ≥18 years of age with HIV infection and clinical evidence of meningitis were prospectively enrolled in the Cryptococcal Optimal Antiretroviral Timing (COAT) Trial (Clinicaltrials.gov: NCT01075152) or in the Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis (ASTRO-CM) trial (Clinicaltrials.gov: NCT01802385) both pilot and randomized trials with enrollees from Uganda between 2010 to 2016.

•They were screened for basic demographics,19 CSF immunologic markers, and antiretroviral use all at baseline

•The participants were evaluated using the Center for Epidemiologic Studies Depression Scale (CES-D). Scores of 16 or greater are considered needing further evaluation for depression. Evaluations were at Week 4 and Week 12.

•Analysis was done comparing those ever depressed with those never depressed. Categorical data was compared using Fisher's Exact Chi-squared test. Numeric data was compared using Wilcoxan Rank Sum Test.

Baseline Characteristics

Distribution of Depression

	Has CES-D	Depressed	Number of visits depressed	N (%)	Depressed At	N (%)
Total	176		**None**	19 (17%)	**Neither visit**	19 (17%)
Week 4	137	99 (72%)	**One**	66 (59%)	**Week 12 Only**	11 (10%)
Week 12	151	57 (38%)	**Two**	27 (24%)	**Week 4 Only**	55 (49%)
Week 4 and Week 12	112		**Ever Depressed**	93 (83%)	**Both Visits**	27 (24%)

Distribution of Biomarkers by Depression Group Among Those With Depression Scores at Week 4 and 12

	Ever Depressed		Never Depressed		
CSF Biomarker, pg/mL	N	Median [IQR]	N	[IQR]	P-value [1]
G-CSF	93	**48.5** [22.6-104]	19	**73.5** [29.9-147]	***0.09***
GM-CSF	93	**315** [223-478]	19	**294** [208-478]	0.83
IFN-g	93	**39.3** [17.1-90.5]	19	**64.0** [16.0-208]	0.14
TNF-a	93	**8.0** [4.0-13.9]	19	**13.9** [3.2-26.0]	0.18
IL-4	93	**1.1** [0.4-2.1]	19	**1.6** [0.6-4.3]	***0.09***
IL-6	93	**169** [45.3-630]	19	**630** [36.8-2195]	0.38
IL-7	93	**3.0** [2.0-6.1]	19	**4.3** [1.5-27.9]	0.44
IL-8	93	**478** [223 -1176]	19	**630** [315-1261]	0.54
IL-10	93	**13.0** [7.5-26.0]	19	**13.0** [7.0-32.0]	0.81
IL-12	93	**5.7** [2.6-10.6]	19	**7.0** [3.0-12.1]	0.83
IL-13	93	**8.0** [2.6-29.9]	19	**9.8** [1.3-52.0]	0.74
IL-17	93	**14.9** [5.7-32.0]	19	**26.0** [8.0-52.0]	0.24
MCP1	93	**416** [194-891]	19	**676** [208-1783]	0.19
CSF WBC, cells/ µL	90	**5** [<4, 90]	19	**<4** [<4, 45]	0.18
Opening Pressure, cm H_20	89	**30** [20, 38]	18	**34** [26, 46]	0.18
CSF Culture, 1000 CFU/mL	84	**75** [4.5, 251]	17	**29.8** [1.7, 438]	0.69

1 Wilcoxon Rank Sum Test

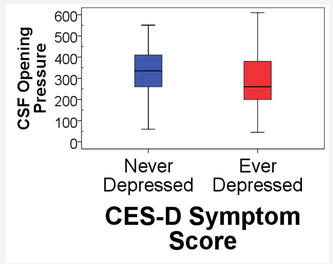
Results

Frequency of Categorical Variables by Depression Group Among Those With Depression Scores at Week 4 and Week 12

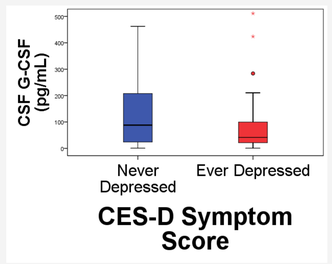
	Ever Depressed		Never Depressed		
Variable at Screening	No. With Data	N (%)	No. With Data	N (%)	P-value[1]
Male gender	93	57 (61.3%)	19	15 (78.9%)	0.15
CSF WBC ≤ 4 / µL	90	45 (50.0%)	19	13 (68.4%)	0.15
OP > 25 cm	89	51 (57.3%)	18	15 (83.3%)	***0.04***
CSF IL2 < 0.55	93	30 (32.3%)	19	8 (42.1%)	0.41

[1] Fisher's Exact Chi-squared test

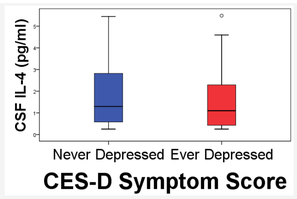
Opening Pressure Higher in Those Never Depressed



G-CSF Higher in Those Never Depressed



IL-4 Higher in Those Never Depressed



Descriptions of Significant Findings

Opening Pressure- a surrogate for intracranial pressure. Idiopathic intracranial hypertension is known to be associated with increased rates of depression.

IL-4 is a pleiotropic cytokine produced by activated T cells. It is a costimulator of DNA-synthesis. It induces the expression of class II MHC molecules on resting B-cells. IL-4 Inhibits IL-1β-Induced Depressive-Like Behavior.

G-CSF granulocyte colony stimulating factor. Known to stimulate the bone marrow to make white blood cells. Administration of G-CSF has been shown to significantly reverse chronic stress-induced depression-like behavior

Results

• 176 participants from meningitis studies had CESD scores completed. 72% depressed at week 4 but only 38% at week 12.

• Those who were ever depressed were not different than those never depressed at baseline in terms of sex, fungal burden and CSF WBC.

• For those ever depressed had *lower*

- •Opening Pressures 300 vs 340 for those never depressed, those with >250 were less likely to ever be depressed (P=0.04)
- •Trended towards lower GCSF (P=0.04)
- •Trended towards lower IL-4 (P=0.04)

Conclusions

•72% with cryptococcal meningitis had depression at week 4 but only 38% at week 12

•Those with depression had lower intracranial pressure at baseline but a similar fungal burden to those without depression.

•Depression was also associated with:

- •1) lower GCSF, a bone marrow stimulating cytokine known to reverse depressive behavior, and IL-4 a B-cell stimulating cytokine produced by T-cells known to inhibit depressive behavior
- •2) lower IL-4, a cytokine made by T-cells which induces B-cells
- •3) lower opening pressure, which is paradoxical given higher given idiopathic intracranial hypertension as well as illness are associated with more depression, however medians of both ever depressed and never depressed are elevated.

•Depression may be associated with the host's immune response to infection, rather than to *Cryptococcus* burden itself.

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