Poster # 2165

# CMV Immunoglobulin G Levels are Associated with Neurocognitive Dysfunction among Adults over Age 50

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## Abstract

**Background:** CMV-infection has been associated with several inflammatory conditions and with increased monocyte/macrophage activation. HIV-associated neurocognitive dysfunction is an incompletely understood inflammatory condition. This study explores the potential role of CMV and monocyte/macrophage activation in neurocognitive dysfunction. **Methods:** Utilizing stored serum specimens from 177 HIV+ and 183 HIV- subjects enrolled in the Rush Center of Excellence on Disparities in HIV and Aging (CEDHA) cohort, quantitative CMV IgG, sCD14, and sCD163 were measured by ELISA. All subjects had previously undergone a battery of neurocognitive tests, including assessment of global cognition (GC) and 5 specific cognitive domains. Spearman correlations and linear regression analyses were used to assess for associations between neurocognitive performance, CMV IgG levels, and monocyte/macrophage activation as measured by sCD14 and sCD163. **Results:** The mean age was 58.7 (SD=6.2) years and mean education level was 13.4 (SD=2.0) years. Mean CD4 count was 621(SD=286) and 97% had undetectable HIV RNA. 166(94%) HIV+ and 135 (73%) HIV- subjects were CMV seropositive. Among all subjects, there was a significant positive correlation between CMV IgG and sCD14 (R=0.16, p=0.002) and CMV IgG and sCD163 (R=0.17, p=0.001). In linear regression models including age, sex, education, HIV status, CMV IgG, sCD163 and sCD14, the following were negatively associated with CMV IgG level: GC (β=-0.004, SE=0.001, p=0.003), episodic cognition (β=-0.005, SE=0.002, p=0.004), semantic memory (β=-0.004, SE=0.002, p=0.02), and visuospatial ability (β=-0.004, SE=0.002, p=0.05). The same models also showed that HIV positive participants had higher levels of GC, episodic memory, semantic memory, working memory, and visuospatial ability. There were no significant associations between sCD14 or SCD163 and cognitive function. **Conclusions:** Among this cohort of older HIV+ and HIV- subjects, higher CMV IgG levels were associated with worse performance on several neurocognitive tests after controlling for age and education level. The potential mechanism of this association is unknown, but findings from this study suggest that it does not involve monocyte/macrophage activation.

## Background

- Cytomegalovirus (CMV) is a herpesvirus that is highly seroprevalent among HIV-positive individuals.
- Following primary infection, CMV establishes a life-long infection by altering the host's innate and adaptive immune responses.
- Higher CMV immunoglobulin G (IgG) levels have been associated with a variety of aging-related diseases, including cardiovascular disease and neurocognitive dysfunction in HIV-positive and HIV-negative persons.
- Soluble CD163 (sCD163) and soluble CD14 (sCD14) are markers of monocyte and macrophage activation that have been associated with various inflammatory conditions, including coronary plaque, other cardiovascular diseases, and neurocognitive dysfunction in patients with HIV infection.
- Among HIV-positive persons, higher CMV IgG levels have been shown to correlate with increased levels of soluble sCD163 and sCD14.
- HIV is known to be associated with a spectrum of neurocognitive deficits referred to as HIV-associated neurocognitive disorders (HAND). Severe dysfunction is much less common in the era of antiretroviral therapy. However, increased rates of mild neurocognitive impairment among HIV-positive patients persist despite effective virologic suppression and may be related to ongoing inflammation.
- In this study, we explore the role of CMV in inflammation and neurocognitive dysfunction in a large cohort of HIV+ and HIV- subjects, using sCD163 and sCD14 as markers of inflammation.

## Materials and Methods

Location:
- All subjects were enrolled in the Rush Center of Excellence on Disparities in HIV and Aging (CEDHA) cohort in Chicago, IL, USA
- CMV IgG, sCD163 and sCD14 measurement was performed at Rush University Medical Center, Chicago, IL, USA

- Study Period: Enrollment for the original CEDHA cohort occurred from January, 2013 through March 2015.
- Study Population: 177 HIV+ and 183 HIV- persons over the age of 50, majority (97%) of HIV+ participants had undetectable HIV RNA
- Data Collected:
  - Demographics and HIV status
  - Neurocognitive function as measured by global cognition score (z-score based on 19 question battery), 5 specific cognitive domain scores (episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability), and quality of life score
  - sCD163, sCD14, and quantitative CMV IgG levels measured by ELISA from stored serum samples
- Statistical Analysis:
  - • Spearman correlations and linear regression analyses were used to assess associations between neurocognitive performance, CMV IgG levels, and monocyte/macrophage activation as measured by sCD14 and sCD163

## Results

### Table 1. Patient Characteristics

| Characteristic | HIV + N = 177 | HIV – N = 183 |
|---|---|---|
| Age, years | 58.7 (SD 5.5) | 58.7 (SD 6.8) |
| Race, n (%) | | |
| Black | 124 (70) | 122 (67) |
| Gender, n (%) | | |
| Male | 134 (76) | 131 (72) |
| Education, years | 13.2 (SD 2.8) | 13.6 (SD 2.9) |
| CMV IgG +, n (%) | 166 (94) | 135 (73) |
| *Quant CMV IgG, IU/mL | 43.2 (SD 21.2) | 25.2 (SD 22.6) |
| sCD14, ng/mL | 1.9 (SD 0.6) | 1.6 (SD 0.4) |
| sCD163, ng/mL | 721.4 (SD 315.2) | 643.8 (SD 307.5) |
| Global Cognition | 0.1 (SD 0.5) | -0.1 (SD 0.6) |
| Episodic Memory | 0.2 (SD 0.6) | -0.1 (SD 0.7) |
| Semantic Memory | 0.1 (SD 0.7) | -0.1 (SD 0.8) |
| Working Memory | 0.1 (SD 0.8) | -0.1 (SD 0.8) |
| Perceptual Speed | 0.01 (SD 0.8) | 0.01 (SD 0.7) |
| Visuospatial Ability | 0.1 (SD 0.9) | -0.1 (SD 0.8) |

Results reported as mean (standard deviation) unless otherwise stated
*Quantitative CMV IgG level among CMV seropositive subjects

**Abbreviations**: CMV, cytomegalovirus; IgG, immunoglobulin; quant, quantitative; sCD14, soluble CD14, sCD163, soluble CD163; SD, standard deviation

### Table 2. Spearman Correlation of CMV IgG and Patient Characteristics

| Characteristic | HIV + subjects N = 177 | HIV – subjects N = 183 | All subjects N = 360 |
|---|---|---|---|
| Age | 0.008 (0.92) | 0.1 (0.07) | 0.09 (0.01) |
| Male Sex | -0.05 (0.48) | -0.31 (<0.0001) | -0.16 (0.002) |
| Education | 0.07 (0.35) | -0.07 (0.36) | -0.03 (0.50) |
| sCD14 | 0.08 (0.26) | -0.04 (0.58) | 0.16 (0.002) |
| sCD163 | 0.11 (0.13) | 0.07 (0.28) | 0.16 (0.001) |
| Global Cognition | -0.09 (0.24) | -0.12 (0.11) | -0.03 (0.63) |
| Episodic Cognition | -0.17 ( 0.03) | -0.04 (0.60) | 0.01 (0.82) |
| Semantic Memory | -0.05 (0.49) | -0.17 (0.03) | -0.07 (0.18) |
| Working Memory | 0.01 (0.85) | -0.12 (0.09) | -0.02 (0.69) |
| Perceptual Speed | -0.04 (0.60) | -0.10 (0.19) | -0.06 (0.23) |
| Visuospatial Ability | -0.02 (0.80) | -0.18 (0.01) | -0.04 (0.45) |

Results reported as correlation coefficient (p-value)
**Abbreviations**: CMV, cytomegalovirus; IgG, immunoglobulin; sCD14, soluble CD14, sCD163, soluble CD163;

### Additional Spearman Correlation Results:

- Among all subjects, both sCD14 and sCD163 had significant positive associations with age (R = 0.20, p = 0.0002 and R = 0.16, p = 0.003 respectively) and HIV positivity (R = 0.33, p = <0.0001, R = 0.16, p = 0.003 respectively).
- Among all subjects there were no significant associations between sCD14 or sCD163 and any of the neurocognitive function domains.

### Table 3. Multivariable Linear Regression* of Factors Associated with Neurocognitive Function

| Characteristic | CMV IgG | sCD14 | sCD163 |
|---|---|---|---|
| Global Cognition | -0.004 (0.001, 0.003) | -0.03 (0.06, 0.66) | 0.0001 (0.0001, 0.22) |
| Episodic Memory | -0.005 (0.002, 0.004) | -0.09 (0.08, 0.21) | 0.0001 (0.0001, 0.56) |
| Semantic Memory | -0.004 (0.002, 0.02) | -0.02 (0.09, 0.85) | 0.0001 (0.0001, 0.29) |
| Working Memory | -0.003 (0.002, 0.15) | 0.02 (0.09, 0.83) | 0.0003 (0.0001, 0.05) |
| Perceptual Speed | -0.003 (0.002, 0.13) | 0.03 (0.09, 0.76) | 0.0000 (0.0001, 0.84) |
| Visuospatial Ability | -0.004 (0.002, 0.05) | -0.006 (0.10, 0.95) | 0.0002 (0.0001, 0.17) |
| Quality of Life, Physical | -0.001 (0.001, 0.24) | 0.09 (0.06, 0.11) | 0.0003 (0.0001, 0.0007) |
| Quality of Life, Mental | -0.0004 (0.001, 0.73) | 0.02 (0.06, 0.78) | 0.0001 (0.0001, 0.25) |

* Variables included in linear regression model: age, sex, education, HIV status, CMV IgG level, sCD14, and sCD163
Results reported as coefficient (standard error, p-value)
**Abbreviations**: CMV, cytomegalovirus; IgG, immunoglobulin G; sCD14, soluble CD14; sCD163, soluble CD163

## Study Limitations

- There are not enough CMV seronegative subjects to allow for comparison of neurocognitive function, sCD163 and sCD14 levels between CMV seropositive and CMV seronegative subjects.
- This is a cross-sectional study and does not assess changes/variability in neurocognitive function over time.
- This study identifies variables associated with neurocognitive function, but does not determine causality.

## Conclusions

- Bivariate analysis does not identify a clear association between CMV IgG level and neurocognitive function. However, in linear regression models accounting for education, age, sex, and HIV status, higher CMV IgG levels are associated with lower neurocognitive performance.
- Linear regression models show that there is no association between sCD14 or sCD163 and global cognition and limited associations between sCD163 and specific cognitive domains.
- These findings suggest that CMV may impact neurocognitive function. However, this association does not appear to rely on monocyte/macrophage activation.
- The role of HIV infection on the relationship between CMV and neurocognition is not clear.
- Further studies are needed to determine if the association between CMV IgG level and neurocognitive function is causal and to explore potential mechanisms for this correlation.

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