Published in final edited form as:

J Neuroimmunol. 2017 October 15; 311: 35–39. doi:10.1016/j.jneuroim.2017.07.014.

Soluble membrane attack complex in the blood and cerebrospinal fluid of HIV-infected individuals, relationship to HIV RNA, and comparison with HIV negatives

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Abstract

The soluble membrane attack complex (sMAC) represents the terminal product of the complement cascade. We enrolled 47 HIV+ adults (12 of whom underwent a second visit at least 24 weeks after starting therapy) as well as 11 HIV negative controls. At baseline, cerebrospinal fluid (CSF) sMAC was detectable in 27.7% of HIV+ individuals. CSF sMAC correlated with CSF HIV RNA levels and was more likely to be detectable in HIV+ individuals on cART compared to HIV negative controls. In HIV+ participants, there were negative association trends between sMAC and neurocognitive performance but these did not reach statistical significance.

Graphical Abstract

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Conflicts of interest:

Theresa N. Schein, CEO / Co-Founder CNine Biosolutions, LLC.
Scott R. Barnum, CSO / Co-Founder CNine Biosolutions, LLC

Keywords

Human Immunodeficiency Virus; Acquired Immunodeficiency Syndrome; Neurocognitive disorder; Complement; Membrane attack complex

1. Introduction

In spite of virologic suppression achievable through combination antiretroviral therapy (cART), infection with the human immunodeficiency virus (HIV) has been linked to a persistent expansion of systemic inflammation (Neuhaus et al., 2010). Of particular significance is the finding that higher systemic inflammation is associated with unfavorable clinical outcomes in HIV-infected individuals, including increased mortality (Duprez et al., 2012). HIV-associated neurocognitive disorders (HAND) remain prevalent in the cART era, and recent research suggests that the development of HAND despite cART may also be in part inflammatory mediated (Heaton et al., 2010, Zayyad and Spudich, 2015).

Dysregulation of adaptive immunity during HIV infection has been long established and aberrant T-cell activation is independently associated with HIV clinical disease progression (Hunt et al., 2011, Liu et al., 1997). While innate immunity dysregulation during HIV infection is less defined, there is mounting evidence that this arm of the immune system is abnormally activated as well. Natural killer cell activation is present in the setting of HIV and does not normalize despite virologic suppression during cART (Lichtfuss et al., 2012). Additionally, activation of the complement system has been recognized since the early years of the HIV epidemic (Liu et al., 2014, Senaldi et al., 1990). It is possible that the complement system plays a role in HIV neuropathogenesis. Non-human primate models have demonstrated upregulation of both C1q and C3 in brain tissue during simian immunodeficiency virus (SIV) infection (Speth et al., 2004). Recent research focusing on young adults with HIV showed a possible association between C1q levels in cerebrospinal fluid (CSF) and both neurocognitive impairment and CSF levels of neurofilament light chain (NFL), an established marker of neuronal damage (McGuire et al., 2016).

The membrane attack complex (MAC) is a large macromolecular protein complex composed of five complement proteins (C5b, C6, C7, C8, and C9) that together generate a pore-forming structure capable of lysing bacteria and other microorganisms (Sonnen and Henneke, 2014). The MAC is assembled when the terminal complement pathway is activated through any of the early pathways (alternative, classical, or lectin) or the extrinsic

protease pathway. Thus, the level of MAC in either soluble (sMAC) or membrane bound form is a marker of terminal complement cascade activity. The MAC also contributes to inflammation through production of ion fluxes and activation of pro-inflammatory signaling pathways in host cells (Morgan, 2016). Elevated CSF sMAC levels have been found to be common in pyogenic bacterial infections of ventricular shunts and to a lesser extent in other neuro-inflammatory diseases such as multiple sclerosis (Ramos et al., 2016, Sellebjerg et al., 1998). In this study, we examined sMAC levels in HIV-infected individuals with varying degrees of neurocognitive impairment in comparison to HIV-negative individuals as well as sMAC change over time in a subset of HIV-infected participants.

2. Methods

2.1 Assessment of participants

Participants were enrolled between March 2011 and January 2017 at the Emory University Center for AIDS Research (CFAR) clinical core site in Atlanta as part of ongoing studies on HIV and neurocognition. Individuals with and without chronic HIV between 18 and 59 years of age were eligible for participation. Individuals were excluded from the study for any of the following: 1) history of any neurologic disease known to affect memory (including stroke, malignancy involving the brain, traumatic brain injury, and AIDS-related opportunistic infection of the central nervous system); 2) current ongoing substance use (marijuana use in the last 7 days OR cocaine, heroin, methamphetamine, or other non-marijuana illicit drug use in the last 30 days); 3) heavy alcohol consumption in the last 30 days (defined as >7 drinks per week for women and >14 drinks per week for men); or 4) serious mental illness including schizophrenia and bipolar disorder (depression was not excluded if participants were well controlled on treatment). HIV+ participants with a history of treated syphilis and a persistently positive rapid plasma regain (RPR) titer of 1:8 or less were eligible for the study if there was a decrease in RPR of at least fourfold at six months after treatment and there were no neurological symptoms at initial syphilis presentation. Lastly, participants were excluded in the event that significant cognitive symptoms had occurred precipitously in the last 30 days in order for further medical workup to be undertaken.

A neuropsychological (NP) battery was administered to the HIV+ participants that included the following nine tests used commonly in studies of cognition and HIV infection (Robertson and Yosief, 2014): 1) Trailmaking Part A; 2) Trailmaking Part B; 3) Hopkins Verbal Learning Test total recall; 4) Hopkins Verbal Learning Test delayed recall; 5) Grooved Pegboard (dominant); 6) Grooved Pegboard (non-dominant); 7) Stroop Color Naming; 8) Stroop Color-Word; and 9) Letter Fluency (Controlled Oral Word Association Test). These tests were selected in order to examine at least five domains as recommended in the most recent nosology of HAND criteria (Antinori et al., 2007). Scores were adjusted for demographic characteristics using published norms (Heaton et al., 2004). Score adjustment for practice effects was also made for longitudinal visits when available by using median practice effect data from previous work (Cysique et al., 2011). A composite neuropsychological test score (NPT-9) was then calculated by average of individual T scores. Global Deficit Score (GDS), a validated measure of neurocognitive impairment in HIV based on demographically

corrected T scores, was calculated and neurocognitive impairment was judged to be present for scores of 0.5 or higher (Carey et al., 2004). The study was approved by the Emory University Institutional Review Board and written consent was obtained from all participants.

2.2 Laboratory assessment

Routine laboratory studies including CD4+ T-lymphocyte counts were performed at the hospital clinical laboratory while HIV RNA levels from plasma and CSF were performed at the Emory Center for AIDS Research (CFAR) virology core using the Abbott laboratories m2000 Real Time HIV-1 assay system (reverse transcriptase polymerase chain reaction). Lowest limit of HIV detection was 40 copies/milliliter (ml). Individuals with no history of HIV infection were confirmed to be negative with the fourth generation Abbott antigen/antibody assay. Soluble MAC was quantitated using the MicroVue complement sC5b-9 Plus enzyme immunoassay (Quidel Corporation) according to the manufacturer instructions. Levels were calculated from a standard curve and the lower limit of detection was 3.7 nanograms (ng)/ml. Samples below the lower limit of detection were assigned a value of one-half lower than the limit of detection as previously described (Ramos, Arynchyna, 2016). Samples were assayed in duplicate and were performed by personnel blinded to all demographic and disease characteristics including whether the sample was from an HIV positive or negative participant.

2.3 Statistical analyses

Analyses were performed with SAS JMP software version 12 and Graphpad prism version 6.07. Normality of variable distribution was assessed with the Shapiro-Wilk test. Given the skewed distribution of most variables, comparisons between continuous variables were performed with the Wilcoxon rank sum test. Comparisons between categorical variables were performed with the chi square likelihood ratio test. For longitudinal paired variable comparison, the Wilcoxon signed rank test was used. For correlations, Spearman's rho test was used for variables that did not meet normality criteria and Pearson's correlation coefficients (r) were generated for variables that met normality criteria. P values for correlation results were adjusted for multiple comparisons using the Bejamini-Hochberg false discovery rate (FDR) correction (Bejamini, 1995). Alpha level for significance was set at <0.05.

3. Results

3.1 HIV+ participants at baseline

There were 47 HIV+ individuals at study entry, 12 of whom had a second longitudinal visit at least 24 weeks after starting cART (total of 59 visits). At baseline (see table 1), 40.4% were already on cART with plasma and CSF HIV RNA level < 40 copies/ml. Forty one of 47 participants (87.2%) had a negative RPR. Twenty one participants (44.7%) had neurocognitive impairment with GDS of greater than or equal to 0.5. Thirteen participants (27.7%) had detectable CSF sMAC at baseline. 10.6% had confirmed hepatitis C virus (HCV) infection with positive serum antibody and detectable plasma HCV RNA, while a separate 4.3% had confirmed hepatitis B virus (HBV) infection with positive HBV surface

antigen and detectable plasma HBV DNA. However, the presence of chronic HBV or HCV was not associated with an increased likelihood of detectable CSF sMAC (37.5% for participants with either hepatitis virus versus 25.6% for participants with neither, $p=0.5$).

3.2 Longitudinal assessment of HIV+ participants

Twelve of the participants off cART had a second visit at least 24 weeks after starting therapy (median 27 weeks, interquartile range 25–30 weeks). Seven of these achieved suppression of plasma HIV RNA and CSF HIV RNA to <100 copies/ml. Despite the fact that not all participants achieved full virologic suppression, there was a significant decrease in plasma sMAC level at the second time point (median 171 ng/ml at time point 1 versus median 153 ng/ml at time point 2, $p=0.034$, see figure 1 for box and whisker plots). Corresponding to this was an improvement in NPT-9 (mean 41.4 for time point 1 versus mean 46.5 for time point 2, $p=0.007$). There was a trend towards decrease in CSF sMAC level at the second time point, but given that a significant proportion of participants had undetectable CSF sMAC at baseline, this did not reach statistical significance ($p=0.11$, see figure 2).

3.3 HIV negative participants compared to virologically suppressed HIV+ subgroup

For this comparison, only HIV+ individuals with a visit on cART for at least 24 weeks with plasma and CSF HIV RNA <100 copies/ml were considered. Additionally, participants who were positive for HCV, HBV or RPR were excluded. Twenty three of the 47 HIV+ participants had one visit that met all of these criteria. Eleven HIV-negative participants who were also confirmed to be negative for HBV surface antigen and HCV antibody were enrolled. Compared to these HIV negative controls, the 23 HIV+ participants were older, more likely to have hypertension, but less likely to smoke tobacco (table 2). While plasma sMAC levels did not differ significantly between the two groups, participants in the HIV+ subgroup were more likely to have detectable CSF sMAC levels than HIV negative participants (22.7% versus 0%, $p=0.04$). The range of detectable CSF sMAC level in this HIV+ subgroup was 3.42–13.91 ng/ml. To further investigate the trend in plasma sMAC difference between HIV+ and HIV-negative participants, we included 11 additional plasma sMAC data points from the HIV+ individuals in the study who had followup visits at least 12 weeks after starting cART (these were not originally included because there was no corresponding CSF sMAC result for these particular visits). This brought the total number of visits for the 47 HIV+ individuals to 70. The median plasma sMAC level for this group as a whole was 138.5 pg/ml with 25%–75% interquartile range= 91–191. When compared to the 11 HIV-negative individuals (median plasma sMAC level= 179 pg/ml, 25%–75% interquartile range= 86–202), the difference was again not significant, this time with a higher p -value (0.32).

3.4 sMAC Correlations in HIV+ participants

When analyzing all HIV+ visits ($n=59$), plasma sMAC levels correlated significantly with CSF sMAC levels ($\rho=0.4$, $p=0.003$) and plasma HIV RNA levels correlated significantly with CSF HIV RNA levels ($\rho=0.81$, $p<0.001$). While the correlation between HIV RNA and sMAC in plasma did not reach statistical significance ($\rho=0.2$, $p=0.09$), there was a significant correlation between HIV RNA and sMAC in CSF ($\rho=0.29$, $p=0.04$). This was

particularly evident when limiting the analysis to the 32 visits at which CSF HIV RNA was detectable ($\rho = 0.79$, $p < 0.001$, see figure two with 80% density ellipse). This was exemplified by the fact that the participant with by far the highest CSF sMAC level (49.5 ng/ml with next highest value of 27.9 ng/ml) also had the highest CSF HIV RNA level (log10 copies/ml of 5.25). There were trends suggesting a negative relationship between NPT-9 and both CSF sMAC and log10 plasma sMAC but these did not reach statistical significance (Spearman's $\rho = -0.14$, $p = 0.29$ and Pearson's $r = -0.25$, $p = 0.11$ respectively). Correlations between sMAC and GDS also suggested associations with worse cognitive performance, but again these were not statistically significant ($\rho = 0.22$, $p = 0.09$ for plasma and $\rho = 0.11$, $p = 0.39$ for CSF).

4. Discussion with conclusions

With the overall population of HIV-infected individuals continuing to increase worldwide (WHO, 2016), it is imperative to better understand the sequelae associated with this infection. Dysregulation of innate immunity in the setting of HIV has been increasingly recognized. The soluble membrane attack complex (sMAC) represents the final product of complement cascade activation and in previous work by investigators from this group and others, sMAC levels in CSF are often elevated within the context of severe neuroinflammatory conditions (Ramos, Arynchyna, 2016, Sellebjerg, Jaliashvili, 1998). In the current study, CSF sMAC was more likely to be detectable in HIV+ individuals compared to HIV negative individuals, even when only including HIV+ individuals on suppressive cART with negative hepatitis and syphilis tests. With recent research demonstrating that CSF HIV RNA is detectable by single copy assay in >40% of individuals on suppressive cART, it is possible that sMAC upregulation could be driven by very low levels of HIV that are not detectable with standard assays (Anderson et al., 2017). Alternatively, systemic sMAC elevation in the setting of HIV could be influenced by microbial gut translocation, which occurs in HIV-infected individuals and appears to be at least in part responsible for the immune activation that occurs despite cART (Brenchley et al., 2006). The significant decrease of plasma sMAC levels after 24 weeks of cART shows that complement activation is at least partially reduced with suppression of HIV. It is possible that a significant decrease in CSF sMAC levels with cART would have also become apparent if a larger number of participants had detectable CSF sMAC prior to therapy initiation.

We acknowledge the limitations of this study. There was an age difference in the HIV+ on cART and HIV negative groups and therefore these two groups were not perfectly matched. Previous research suggests that concentrations of some CSF proteins can vary by age. A study by of 107 individuals of varying age showed a positive relationship between advancing age and CSF alpha-2-macroglobulin, but a non-significant relationship between age and CSF albumin or IgG. (Garton et al., 1991) Another study showed that CSF/serum albumin ratio, a surrogate for blood-brain barrier integrity, is more variable in older individuals. (Blennow et al., 1993) Thus, the blood brain barrier may change with advancing age. In our study, this could contribute to the finding that the HIV+ group was more likely to have detectable CSF sMAC levels. When including all 71 visits with CSF protein and sMAC values available, we found a significant positive correlation between age and CSF protein ($\rho = 0.5$, $p < 0.001$) but

a non-significant correlation between age and CSF sMAC ($\rho=0.18$, $r=0.13$). More research is needed that includes strict matching between groups based on demographic and disease data.

Also, there was a trend towards lower blood sMAC concentration in HIV-infected individuals on cART. However, this result was not statistically significant. Our inclusion of additional visits among the HIV-infected participants narrowed this possible difference in plasma sMAC concentration. However, given the trend, studies with larger groups of individuals are indicated in order to confirm this finding.

While all HIV+ participants on cART had been on treatment for over 24 weeks in this subgroup analysis, it is possible that if individuals with much longer periods of virologic control were included that no difference in CSF sMAC detectability compared to HIV negative controls would be observed. Given the significant relationship between plasma and CSF sMAC, it is possible that the elevated levels found in certain individuals reflect systemic complement activation as opposed to a central nervous system (CNS) specific effect. HIV infection is associated with disruption of the blood brain barrier (Toborek et al., 2005) and it is possible that sMAC may diffuse into the CNS in this setting. We also acknowledge that this is a relatively small study and the negative associations between sMAC levels and neurocognitive performance did not reach statistical significance. Additionally, our neurocognitive test panel did not assess all domains, including visual memory. Therefore it is not currently clear if an abnormally activated complement system during HIV has clinical implications. However, a recently published study focusing on young HIV-infected adults showed a possible association between increased complement expression (specifically C1q) and neurocognitive impairment (McGuire, Gill, 2016). Combining these results with the current study, more research is indicated. A larger study will likely be needed to determine if sMAC specifically or complement activation more generally could be linked to neurocognitive impairment among HIV-infected individuals.

Acknowledgments

Funding sources:

Emory Medical Care Foundation

NIH K23MH095679

NIH P30 AI050409 (Emory Center for AIDS Research)

Impact Fund of Children's of Alabama

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Highlights

- This is a study of the soluble membrane complex (sMAC) in paired CSF/plasma samples from 47 HIV-infected individuals (12 of whom had longitudinal visits after starting cART) as well as 11 HIV-negative individuals.
- CSF sMAC levels were found to be detectable at baseline in 27% of HIV+ participants.
- Even when including only those on suppressive cART, HIV+ participants were more likely to have detectable CSF sMAC compared to HIV-negative participants.
- CSF sMAC levels correlated significantly with CSF HIV RNA levels.
- Plasma sMAC levels declined significantly during antiretroviral therapy.
- There was a negative association trend between sMAC and cognitive performance that warrants further investigation.

Figure 1.
Significant decrease in plasma sMAC concentration after 24 weeks of combination antiretroviral therapy (central line denotes mean)

Figure 2.
CSF sMAC levels Visit 2= 24 weeks after cART initiation

Fig. 3.

Table 1
Baseline HIV+ participant demographic and disease characteristics

Variable (N=47)	Median (IQR) or Number (%)
Age in years	45 (36–50)
Male sex	40 (85.1%)
Race	
African-American	35 (74.5%)
White	11 (23.4%)
Native-American	1 (2.1%)
Years of HIV infection	8 (2–20)
Co-morbidities	
Cigarette smoker	23 (49%)
Hypertension	7 (14.9%)
Hepatitis C infection	5 (10.6%)
Diabetes mellitus	4 (8.5%)
Hepatitis B infection	2 (4.3%)
on cART with suppressed plasma/CSF HIV RNA	19 (40.4%)
Laboratory results (plasma)	
CD4 count (cells/ μ l)	201 (51–415)
CD4%	20 (7–25)
CD4 nadir	55 (22–149)
Log10 Plasma HIV (detectable n=28)	5.2 (4.2–5.6)
ANC	2.2 (1.48–3.23)
Creatinine (mg/dl)	0.9 (0.8–1.1)
Plasma MAC (ng/ml)	138 (105–191)
Laboratory results (CSF)	
WBC (cells/ μ l)	0 (0–3)
RBC (cells/ μ l)	0 (0–1)
Protein (mg/dl)	38 (30–51)
Log10 CSF HIV (detectable n=27)	3.23 (2.61–3.99)
CSF MAC (detectable n=13)	8.36 (3.82–19.36)
Neuropsychological testing	
NPT-9	45.3 (40.2–50.7)
GDS	0.38 (0.0–0.78)

Abbreviations: IQR=interquartile range; HIV=human immunodeficiency virus infection; cART= combination antiretroviral therapy; CSF= cerebrospinal fluid; CD= cluster of differentiation; μ l= microliter; ANC= absolute neutrophil count, reported as cells $\times 10^3$; MAC= membrane attack complex; mg= milligrams; dl=deciliter; ng= nanograms; CSF= cerebrospinal fluid; WBC= white blood cell count; RBC= red blood cell count; NPT= Neuropsychological composite T score; GDS= global deficit score

Table 2
Comparisons between HIV positive and negative groups

HIV+ group limited to participants on cART with plasma/CSF HIV RNA<100 who were negative for hepatitis C, hepatitis B, and RPR

Variable Median (IQR) or Number (%)	HIV+ (n=23)	HIV negative (n=11)	P value for difference
Age in years	48 (42–50)	35 (31–48)	0.02
Male sex	20 (87%)	9 (82%)	0.7
Race			0.5
African-American	15 (65.2%)	9 (81.8%)	
White	7 (30.4%)	2 (18.2%)	
Other	1 (4.3%)	0 (0%)	
Co-morbidities			
Cigarette smoker	8 (35%)	8 (72%)	0.04
Hypertension	7 (30%)	0 (0%)	0.01
Diabetes mellitus	3 (13%)	0 (0%)	0.12
Laboratory results (plasma)			
Hemoglobin	14.8 (13.4–15.3)	14.9 (13.8–15.4)	0.6
ANC	3.0 (2.1–4.0)	3.6 (2.2–4.4)	0.6
Plasma MAC (ng/ml)	128 (105–158)	179 (86–202)	0.11
Laboratory results (CSF)			
WBC (cells/μl)	0 (0–3)	0 (0–0)	0.13
RBC (cells/μl)	0 (0–1)	0 (0–3)	0.48
Protein (mg/dl)	39 (32–54)	30 (23–37)	0.01
Detectable CSF MAC	5 (22.7%)	0 (0%)	0.04

Abbreviations: IQR=interquartile range; HIV=human immunodeficiency virus infection; cART= combination antiretroviral therapy;; μl= microliter; ANC= absolute neutrophil count, reported as cells × 10³; MAC= membrane attack complex; mg= milligrams; dl=deciliter; ng= nanograms; CSF= cerebrospinal fluid; WBC= white blood cell count; RBC= red blood cell count; NPT=Neuropsychological composite T score;

* denotes p value <0.05