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Clinical Science Workshop 2

# HIV—dementia

Chairpersons: G. Arendt (Düsseldorf, D)
J. Berger (Lexington, USA)

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### Individuals co-infected with hepatitis C (HCV) and HIV are more cognitively impaired than those infected with either virus alone

*S. Letendre, M. Cherner, R. Ellis, T. Marcotte, R. Heaton, J.A. McCutchan, I. Grant*
University of California (San Diego, USA)

Background: HCV can cause neurologic disease, including cognitive and mood disorders. HCV primarily infects hepatocytes but can infect monocyte-derived macrophages (MDM), which are important in HIV neuropathogenesis. Since HIV and HCV co-infection is common, HCV may contribute to HIV-associated neural injury.

Methods: We evaluated subjects in a study of the CNS effects of methamphetamine (meth), many of whom were infected with HIV and HCV. Subjects are recruited into 4 groups, defined by HIV infection (HIV+ or HIV−) and meth dependence (meth+ or meth−). Meth+ subjects met criteria for meth-dependence within a year but were not actively using meth, heroin, or cocaine. We measured HCV IgG by ELISA in 174 subjects (41 HIV–meth–, 39 HIV+ meth–, 61 HIV–meth+, and 33 HIV + meth+). The groups were similar except that HIV+ subjects were more likely to be men and meth– subjects were better educated. All subjects underwent standardized neuropsychological and neuromedical assessments, including lumbar puncture. HIV and HCV RNA levels were measured in plasma and CSF by RT-PCR.

Results: HCV IgG was detected in 33 (19%), 31 (94%) of whom were meth+. Compared with HCV– subjects, HCV+ subjects were 4 times more likely to test impaired (OR = 4.1, p = .0004). Their overall test performance was worse (median global deficit score (mGDS) .74 vs .32, p = .0001), even after adjusting for HIV, meth, and antiretroviral (ARV) status. Impairment was most pronounced in co-infected subjects (n = 14, mGDS .90) compared to those infected with HCV alone (n = 19, mGDS .63), HIV alone (n = 58, mGDS .42), or neither (n = 83, mGDS .26) (p = .0005). HCV RNA levels varied widely in plasma (median 400,000 copies/mL, IQR 650-3,100,000) but were below 100 copies/mL in all CSF specimens. After adjusting for ARV use, those with plasma HCV RNA levels greater than 1,000,000 had higher levels of HIV RNA in CSF, but not in plasma.

Conclusions: HIV and HCV are common co-pathogens and may synergistically cause neural injury. HCV may mediate neural injury by infecting or activating MDMs, which may then migrate into the brain. Once there, HCV-activated MDMs may release neurotoxins and upregulate HIV replication.

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### CNS invasion by CD14+/CD16+ peripheral blood-derived monocytes in HIV dementia: perivascular accumulation and reservoir of HIV infection

*T. Fischer-Smith,[1] S. Croul,[1] A. Sverstiuk,[1] C. Capini,[1] D. L'Heureux,[1] E. Regulier,[1] M. Richardson,[1] S. Amini,[1] S. Morgello,[2] K. Khalili,[1] J. Rappaport[1]*
1. Center for Neurovirology and Cancer Biology (Philadelphia, USA)
2. Mount Sinai School of Medicine (New York, USA)

Increases in circulating CD14+/CD16+ monocytes have been associated with HIV dementia; trafficking of these cells into the CNS has been proposed to play an important role in the pathogenesis of HIV-induced neurological disorders. This model suggests that events outside the CNS leading to monocyte activation initiate the process leading to HIV dementia. To investigate the role of this activated monocyte subset in the pathogenesis of HIV dementia, we examined brain specimens from patients with HIV encephalitis (HIVE), HIV without encephalitis and seronegative controls. Immunohistochemical staining demonstrated an accumulation of perivascular macrophages in patients with HIVE. The majority of these cells identified in microglial nodules and in the perivascular infiltrate were CD14+/CD16+. P24 antigen co-localized with both CD14 and CD16, suggesting that the CD14+/CD16+ macrophage is a major reservoir of HIV-1 infection in CNS. CD45/LCA staining allowed us to differentiate the perivascular macrophage from resident microglia. In addition to perivascular and nodular localizations, CD16 also stained ramified cells throughout the white matter. These cells were more ramified and abundant than cells positive for CD14 in white matter. Double staining for p24 and CD16 suggests that these cells were often infected with HIV-1.

The prominent distribution of CD14+ cells in HIVE prompted our analysis of soluble CD14 (sCD14) levels in CSF. ELISA assay revealed the presence of higher levels of sCD14 in patients with moderate to severe HIV dementia, suggesting the utility of sCD14 as a surrogate marker.

Although the importance of the circulating CD14+/CD16+ monocyte subset in HIV dementia has been proposed, there have been no studies in human CNS tissue to directly examine this hypothesis. In the studies presented here, we provide clear evidence for CNS accumulation of CD14+/CD16+ cells, many of which are HIV-1 infected, in HIVE. These CD14+/CD16+ monocytes may play a role in other neurological disorders and sCD14 may be useful for evaluating these conditions.

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## The relationship between viral load response to highly active antiretroviral therapy and psychomotor speed performance in HIV+ homosexual men

*N. Sacktor,[1] R. Skolasky,[2] P. Tarwater,[3] J. McArthur,[2] O. Selnes,[2] J. Becker,[4] B. Cohen,[5] E. Miller[6]*
1. Johns Hopkins Bayview Campus
2. Johns Hopkins Hospital
3. Johns Hopkins School of Public Health
4. University. of Pittsburgh Medical Center
5. Northwestern University Medical School
6. Univ. of California
a Multicenter AIDS Cohort Study (USA)

Introduction: Highly active antiretroviral therapy (HAART) is effective in suppressing plasma viral load and decreasing the incidence of HIV dementia. However, the precise relationship between a virological response to HAART (or subsequent rebound) and cognitive performance remains unclear.

Objective: To determine whether a viral load response to HAART among HIV+ individuals was associated with improvement on two tests of psychomotor speed (a sensitive index of HIV dementia) and whether a virological rebound was associated with cognitive deterioration.

Methods: Fifty-one HIV+ homosexual men initiating HAART with cognitive impairment [defined as a 1 SD abnormality on either the Symbol Digit Modalities Test (SDMT) or the Trail Making Test Part B (TM)] were studied longitudinally within the Multicenter AIDS Cohort Study. A virological response was defined as a 1 log reduction or transition to undetectable plasma HIV viral load within one year of initiating HAART. Responders were compared to "non-responders" on the two tests of psychomotor speed. Subjects who subsequently had a virological rebound, defined as a 1 log increase in viral load, were then compared to "non-rebounders."

Results: Thirty of 51 subjects had virological suppression. Viral load responders had an improved SDMT Z score (change in Z score = 0.56, $p < 0.05$) and TM Z score (change in Z score = 0.72, $p < 0.05$). There was no improvement among non-responders (change in SDMT Z score = 0.16; TM Z score = 0.44). Viral load rebounders (n = 11) deteriorated in the TM Z score (change from pre rebound visit to rebound visit = −0.75) whereas non-rebounders remained stable (change = 0.02) ($p < 0.05$). SDMT Z score changes also showed deterioration among viral load rebounders (change = −0.21) compared to non-rebounders (change = 0.03) ($p < 0.05$).

Conclusion: In HIV+ individuals with cognitive impairment viral load suppression in response to HAART was associated with improved psychomotor speed performance, and virological rebound was associated with deterioration in psychomotor speed performance compared to individuals without a virological rebound.

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## MR predictors of HIV dementia

*M.J. Avison, A. Nath, R.G. Avison, R.A. Bales, R. Greenberg, F.A. Schmitt, J.R. Berger*
University of Kentucky (Lexington, USA)

Objective: To examine the roles of inflammatory and non-inflammatory pathways of subcortical damage in the pathogenesis of HIV dementia (HIVD).

Background: Evidence exists for direct neurotoxicity of HIV via non-inflammatory pathways, and indirect neurotoxicity through activation of inflammatory pathways. The relative importance of inflammatory and non-inflammatory pathways to HIVD pathogenesis is unclear. Variation in their relative activities may underlie the variable onset, severity and response to therapy of HIVD from patient to patient.

Design/methods: 17 HIV+ patients underwent neurologic (Powers HIVD Score) and neuropsychological (MACS NPZ8) examination. NAA/Cr (index of neuronal integrity) and Cho/Cr (index of cellularity/gliosis) ratios were measured in the basal ganglia (BG) and frontal white matter (FWM) by 1H-MRS. Fractional enhancement on T1-weighted MRI 30 minutes post-contrast (FE30) was measured to assess microvascular integrity in BG and FWM. CSF levels of monocyte chemoattractant protein-1 (MCP-1) were also measured.

Results: 1) BG NAA/Cr was a significant predictor of neurologic (Powers, $R^2 = 0.49$, $p = 0.005$) and neuropsychologic performance (NPZ8, $R^2 = 0.29$, $p = 0.05$).

2) BG FE30 was a significant predictor of neurologic performance (Powers, $R^2 = 0.48$, $p = 0.006$) and neuropsychologic performance (NPZ8, $R^2 = 0.29$, $p = 0.05$).

3) BG FE30 was significantly correlated with MCP-1 ($R^2 = 0.4$, $p = 0.04$).

4) MCP-1 was a significant predictor of neurologic (Powers, $R^2 = 0.49$, $p = 0.0006$) and neuropsychologic performance (NPZ8, $R^2 = 0.495$, $p = 0.03$).

5) BG NAA/Cr and BG FE30 were not correlated ($R^2 = 0.15$, $p = 0.19$).

Conclusions: NAA/Cr and FE30 in the BG are independent predictors of HIVD status, suggesting that the metabolic and microvascular changes may have different pathogenic origins. Consistent with this view, BG FE30 was correlated with CSF MCP-1, an inflammatory marker which was itself a significant predictor of HIVD status, while NAA/Cr was not. These data suggest a multifactorial model of HIVD pathogenesis, with both inflammatory and non-inflammatory axes.

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