Abstract # 488

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Abdominal Obesity, Inflammation, Immune Activation and Neurocognitive Impairment

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CHARTER
CNS HIV Anti-Retroviral Therapy Effects Research
CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Background and Significance

Nearly half of well-controlled HIV patients are neuro-cognitively impaired (**NCI**). We have previously shown that waist circumference (**WC**) is correlated with NCI and now hypothesize that inflammation in abdominal fat and associated metabolic abnormalities could mediate immune activation and inflammation, thereby contributing to NCI.

Specific Aims

In patients with well-controlled HIV infection, to determine if

Aim 1: Systemic inflammation and CNS immune activation modify the risk of NCI in obese HIV⁺ persons.

Aim 2: CSF sCD40L (a marker of immune activation) is elevated in patients with systemic inflammation and NCI.

Design

- **Cross-sectional study** of **CHARTER patients** with existing neuro-medical and neuro-psychological data.
- **Study population** included **152** CHARTER patients with:
  - Plasma HIV RNA < 1000 copies/ml
  - GDS testing at index visit & proximate 6mo visits ±1 yr
  - No history of CNS "confounding" conditions
  - Plasma and CSF samples available at index visit

Measures and Methods

Abdominal Obesity: WC ≥88cm in women; ≥102cm in men
Neurocognitive Assessment: Global deficit score (GDS) is a summary of performance testing in 7 cognitive domains compared to norms adjusted for age, race-ethnicity and education; GDS is abnormal if the total score is ≥0.5.
Biomarkers:
• Plasma assays for hsIL-6, sCD14, and sCD163
• CSF assays for sTNFrII, MCP-1, MMP-9, sICAM, sCD40L
Statistical Analyses:
• Between group comparisons (T tests for parametric and Wilcoxon rank sum tests for nonparametric data)
• Correlation analyses (Pearson and Spearman)
• Regression analysis and ANOVA
• Path analysis for predictors and mediators of GDS

Results

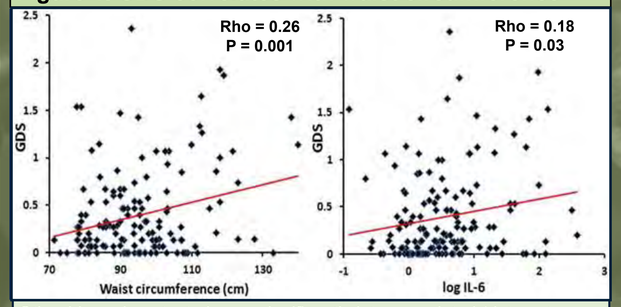
Table 1. Patient Characteristics for the Total Study Cohort and for Obese versus Non-obese Patients.

	Total Cohort (n=152)	Non-obese (N=101)	Obese* (N=51)	P value**
Demographics				
Age, years	49.1±8.1	48.8±7.8	49.7±8.6	0.55
Smoking ever (%)	120 (79%)	78 (77%)	42 (82%)	0.47
IV drug use ever (%)	38 (25%)	39 (29%)	9 (18%)	0.14
CMV antibody positive (%)	5.5±4.4	5.5±4.3	5.7±4.6	0.74
HIV Disease Status				
Duration HIV Infection yrs	14.5±6.3	14.8±6.2	14.1±6.4	0.52
Current CD4[3] *cells/mm*[3]	611±368	570±310	694±455	0.09
Nadir CD4[3] *cells/mm*[3]	147±143	148±157	144±111	0.83
Plasma VL *c/mL* (log_{10})	1.8±0.3	1.8±0.3	1.7±0.2	**0.03**
Plasma VL undetectable	124 (82%)	80 (79%)	44 (86%)	0.29
CSF VL detectable (%)	10 (7%)	8 (8%)	2 (4%)	0.35
Metabolic parameters				
Systolic pressure *mm Hg*	125±15	126±15	123±15	0.31
LDL-C *mg/dL*	101±35	97±35	110±32	**0.03**
HDL-C *mg/dL*	50±19	52±20	48±18	0.23
Triglycerides *mg/dL*	181±131	170±118	203±152	0.18
HOMA-IR	5.0±12.0	4.0±13.0	6.0±7.0	**0.002**
Neurocognitive Impairment				
Global deficit score GDS	0.39±0.4	0.33±0.42	0.53±0.53	**0.02**
Impaired by GDS (%)	43 (28%)	21 (21%)	22 (43%)	**0.004**

* WC for women ≥88cm, for men ≥102cm; ** obese vs non-obese cohorts

Thus, abdominally-obese patients were more likely to be **cognitively impaired** = **Global Deficit Score ≥0.5**

Figure 1. GDS correlates with waist circumference



Other biomarkers tested were significantly inter-correlated (data not shown) but only WC and IL-6 were related to GDS (Pearson's correlation)

Results

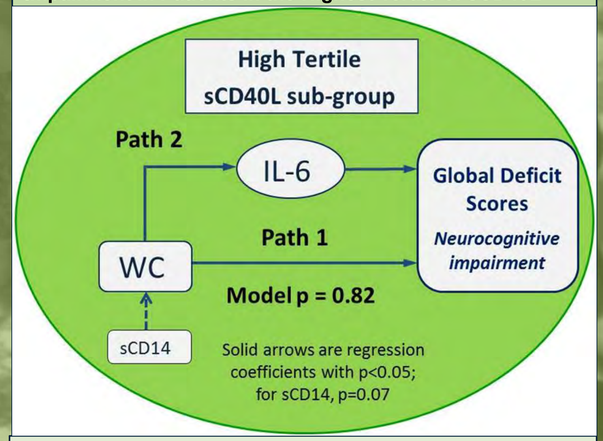
Table 2. Correlations of WC and IL-6 to GDS depend on levels of other biomarkers

	WC vs GDS Rho=0.26, p=0.001		IL-6 vs GDS Rho=0.18, p=0.03	
	High tertile	Low tertile	High tertile	Low tertile
Plasma IL-6	**r = 0.39* (p=0.005)**	r = -0.07 (p=0.65)	NA	NA
CSF sCD40L	r = 0.37 (p=0.007)	r = 0.18 (p=0.20)	**r = 0.60* (p<0.0001)**	r = 0.01 (p=0.93)

* P<0.05 for high vs low tertile

Of the biomarkers, CSF sCD40L, a marker of CNS immune activation, was most affected the relationship of IL-6 to GDS.

Figure 2 . Pathway Model of Mediators of Neurocognitive Impairment in Patients in the Highest Tertile of sCD40L



The **Path Analysis** shows that the data fits the model well based on the high p value (0.82) and that:

- IL-6 mediates the effects of WC on GDS (path 2)
- WC directly affects GDS (path 1) independently of IL-6
- The best model is in subjects with high CSF sCD40L, since WC and IL-6 have the greatest impact on GDS in these patients.

Results

Table 3. High IL-6 levels predict increasing cognitive impairment*
GDS slopes from ≥3 semiannual NP assessments ±1 year of the index visit

	High IL-6 tertile	Low IL-6 tertile	Δ in slopes
GDS slope*	rho = +0.28 p = 0.06	rho = -0.25 p = 0.11	p = 0.02

* Positive slope reflects worsening NC function and negative slope improving function

Table 4. Neurocognitive Function by Gender and Abdominal Obesity

	non-Ob WOMEN N=7	Obese WOMEN N=16	P *	non-OB MEN N=94	Obese MEN N=35	P *	P * Obese W v M
Global Deficit Score	0.10±0.11	0.30±0.36	**.05**	0.34±0.43	0.63±0.57	**.01**	**.04**
Impaired by GDS (%)	0 (0%)	5 (31%)	.27	21 (22%)	17 (49%)	**.004**	.25
SBP, *mm Hg*	117±15	111±15	.43	126±15	128±11	.54	**<.001**
Cholesterol, *mg/dL*	165±39	207±33	**.02**	183±39	187±33	.63	**.05**
HDL-C, *mg/dL*	61±22	62±16	.86	51±20	41±14	**.003**	**<.001**
Triglycerides, *mg/dL*	126±54	118±50	.72	173±122	243±168	**.01**	**.002**
HOMA-IR	1.10±0.28	3.04±3.08	**.05**	4.72±13.6	6.95±7.99	**.31**	**.03**
Adiponectin, *ng/mL10³*	6.3±3.7	5.1±2.4	.45	4.6±3.0	3.3±1.4	**.002**	**.03**

* t test for continuous variables; for GDS 2-way ANOVA p=0.008 for gender & p=0.003 for obesity

Obese men are more cognitively impaired and metabolically abnormal than obese women, supporting a metabolic pathway from WC to NCI.

Summary and Conclusions

- Abdominal obesity (WC) is directly related to NCI by path 1 (Fig. 2).
- Abdominal obesity confers greater risk of NCI in men than women.
- In these obese men, high blood pressure, dyslipidemia, and insulin resistance (i.e. metabolic syndrome) could mediate NCI by path 1.
- Systemic inflammation (elevated IL-6) appears to mediate part of the the effect of abdominal obesity (WC) on NCI by path 2 (Fig. 2).
- High IL-6 is associated with worsening NC function over time (Table 3)
- CNS immune activation (elevated CSF sCD40L) and impaired GDS are linked to systemic inflammation (IL-6) in patients with increased WC.

Future Directions

- If these findings are validated in a larger prospective study, treatment strategies to 1) reduce inflammation and 2) treat components of the metabolic syndrome should be developed.

CHARTER NEUROAIDS DATA RESOURCE

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