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Peripheral Endothelial Glycocalyx Degeneration Is Associated With White Matter Compromise in HIV

Kalpana J. Kallianpur[1], Melissa Agsalda-Garcia[1], Thomas Clausen[1], Neda Jahanshad[2],Talia Nir[2], Alan Garcia[1], Dominic Chow[1], Cecilia Shikuma[1]
[1]Hawaii Center for AIDS, University of Hawaii, Honolulu, HI, U.S.A.; [2]Keck School of Medicine, University of Southern California, Los Angeles, U.S.A.

BACKGROUND

HIV-associated neurocognitive disorders remain prevalent worldwide, even among individuals on antiretroviral therapy (ART)[1]. The endothelial glycocalyx plays a major role in maintaining the blood-brain barrier (BBB) and vascular health. Injury to the glycocalyx, often seen in infectious or inflammatory conditions, may disrupt BBB function[2]. We examined two peripheral markers of glycocalyx degradation, hyaluronic acid (HA) and syndecan-1, for associations with brain structure with a view to understanding neuropsychological (NP) impairment in HIV.

METHODS

- 53 people with HIV (PWH) and 75 HIV-negative controls were drawn from the Hawaii Aging with HIV Cohort–Cardiovascular Disease study and a separate study, respectively. Of these, *glycocalyx data were available for 52 PWH and 75 HIV- individuals*. Our study sample comprised those who also underwent brain imaging and NP testing: **52 PWH and 57 HIV- controls** (Table 1)

Table 1. Demographic and clinical characteristics of study population

Variable	People with HIV (N=52)	HIV-negative (N=57)	p
Age (years)	51.6 ± 7.2	54.2 ± 7.4	0.07
Male gender	44 (86%)	44 (77%)	0.33
Education (years)	15.4 ± 2.5	14.4 ± 2.3	0.03
Race (Caucasian)	29 (57%)	39 (68%)	0.17
Current CD4 count (cells/mm^3)	459.1 ± 218.1	—	—
Nadir CD4 count (cells/mm^3)	153.5 ± 135.9	—	—
Undetectable HIV RNA (≤ 48 copies/mL)	42 (82%)	—	—

Values are given as mean ± SD or N (%). P-values were computed by two-sided t-test (continuous variables) or χ^2 test (categorical variables).

- Syndecan-1 and HA were quantified in serum by ELISA; NP test z-scores were obtained using an HIV-specific battery[3] (Table 2).

Table 2. Neuropsychological (NP) test performance and glycocalyx degeneration markers for people with HIV (PWH) and HIV-negative controls

Glycocalyx markers	PWH (N=52)	HIV-negative (N=75)†	p
Syndecan-1 (ng/mL)	68.7 (32.5-586.8)	68.5 (27.0-13,513.5)	0.54
Hyaluronic acid (ng/mL)	79.5 (19.6-1549.3)	58.7 (8.3-341.1)	<0.001
NP domain z-scores	PWH (N=52)	HIV-negative (N=57)	p
Learning and memory	-0.283 ± 1.027	0.081 ± 0.944	**.063**
Psychomotor speed	0.214 ± 0.682	0.201 ± 0.893	.934
Executive function	0.077 ± 1.036	0.221 ± 1.121	.493
Working memory	-0.173 ± 0.793	0.251 ± 0.885	**.010**
Global_14	-0.138 ± 0.610	0.123 ± 0.614	**.036**

NP z-scores are expressed as mean ± SD, and glycocalyx markers as median (min–max). P-values were computed by two-sided t-test (NP scores) and Mann-Whitney test (glycocalyx markers).
†For the sub-sample of 52 PWH and 57 HIV-negative individuals, p=0.006 for HA; median HA is 75.6 (PWH) and 62.7 (controls). P=0.44 for syndecan-1.

- Brain magnetic resonance imaging (MRI) at 3T was performed once to acquire anatomical MRI and diffusion tensor imaging (DTI) data. T1-weighted scans were processed with FreeSurfer to obtain regional volumes and intracranial volume (ICV); DTI data yielded average fractional anisotropy (FA) and mean diffusivity (MD) in left and right hemispheres (LH, RH) and total (LH+RH) regions[4]. *Controls: DTI measures were not available .*

People with HIV showed impaired working memory and global neuropsychological functioning.

Elevated blood markers of glycocalyx degradation were associated with macrostructural and microstructural white matter damage in brain structures crucial to memory.

Glycocalyx degeneration may compromise white matter integrity, resulting in NP impairment despite suppressive ART.

RESULTS

1. PWH performed worse than HIV- controls in working memory and global NP function (Table 2; Figure 1).

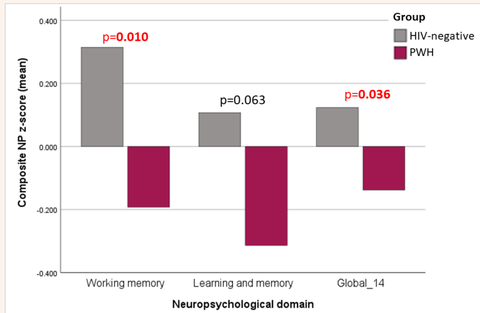


Figure 1. NP test performance in people with HIV (PWH) and HIV-negative controls. P-values were computed by t-test.

Syndecan-1 and HA levels did not correlate with NP z-scores.

3. ANCOVA with HIV group as the factor, a glycocalyx marker as predictor, and age and ICV as covariates showed higher HA to be significantly associated with smaller corpus callosum and cortical white matter volumes (Table 3).

Table 3. Associations between regional brain volumes and HA

Brain region (volume)	Predictor variables	β	p
Corpus callosum	HIV status	0.18	0.077
	Age	-0.22	0.024
	ICV	0.11	0.228
	Hyaluronic acid	-0.28	**0.006**
Cortical white matter	HIV status	-0.003	0.092
	Age	-0.23	<0.001
	ICV	0.73	<0.001
	Hyaluronic acid	-0.14	**0.038**
Pallidum	HIV status	0.02	0.803
	Age	-0.33	<0.001
	ICV	0.47	<0.001
	Hyaluronic acid	-0.17	0.053

Associations were assessed by linear regression and ANCOVA. Standardized beta (β) coefficients and p-values are shown.

2. PWH demonstrated significantly elevated HA (Figure 2).

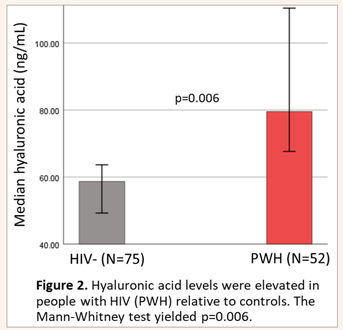


Figure 2. Hyaluronic acid levels were elevated in people with HIV (PWH) relative to controls. The Mann-Whitney test yielded p=0.006.

4. In PWH, higher syndecan-1 and HA correlated with lower FA in multiple brain regions (Table 4).

Table 4. Correlations of glycocalyx markers with DTI indices averaged over brain regions in PWH.

Marker	DTI index	Brain region	ρ	p
HA	FA	Fornix, RH	-0.33	0.018
HA	FA	Fornix, total	-0.32	0.023
Syndecan-1	FA	Hippocampus, LH	-0.31	0.024
Syndecan-1	FA	Hippocampus, RH	-0.27	0.055
Syndecan-1	FA	Hippocampus, total	-0.31	0.028
Syndecan-1	FA	Body of CC, LH	-0.29	0.032
Syndecan-1	FA	Body of CC, total	-0.29	0.038
Syndecan-1	FA	Entire CC, total	-0.25	0.074
Syndecan-1	FA	Fornix, LH	-0.27	0.054
Syndecan-1	MD	Body of CC, total	0.26	0.062

Spearman coefficients (ρ) and p-values are given. HA=hyaluronic acid; CC=corpus callosum; FA=fractional anisotropy; MD=mean diffusivity; RH (LH)=right (left) hemisphere; total=LH+RH.

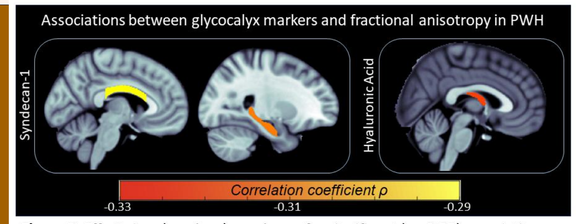


Figure 3. Effect sizes (ρ-values) are shown for significant (p< 0.05) associations between regional FA values and syndecan-1 *(left)* and hyaluronic acid *(right)*.

(Effects shown are for FA averaged across both hemispheres; see Table 4 for lateral effects.)

Figure 3 depicts significant correlations between regional FA and glycocalyx markers. On the left, higher syndecan-1 is associated with lower FA in the CC body and the hippocampus. The right panel shows a negative association between HA and fornix FA.

CONCLUSIONS

- PWH exhibited impaired working memory and associations between elevated HA and smaller WM volumes.
- Higher circulating HA and/or syndecan-1 in PWH were linked to microstructural damage in the corpus callosum hippocampus, and fornix, which play important roles in working memory.
- The fact that glycocalyx markers did not correlate with NP z-scores suggests that endothelial injury may occur upstream of structural brain changes and measurable cognitive decline.
- Glycocalyx degeneration in HIV may compromise the integrity of brain white matter, which in turn may relate to the persistence of NP impairment despite suppressive ART.
- *Limitations:* (i) As the study was cross-sectional, associations found here do not necessarily indicate causality; (ii) we used FA and MD values averaged over selected brain regions.
- Future work will include *whole-brain voxelwise analyses* of DTI measures and glycocalyx degeneration markers.

ADDITIONAL INFORMATION

References:
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Corresponding author: K.J. Kallianpur, kalpana@hawaii.edu
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