ENDOTHELIAL ACTIVATION AND INFLAMMATION ASSOCIATED WITH MICROSTRUCTURAL WHITE MATTER INJURY AND POOR VISUOMOTOR INTEGRATION IN HIV-INFECTED CHILDREN

C. BLOKHUIS[1], M. VAN ZANTEN[1], S. COHEN[1], H.J. SCHERPBIER[1], H.J. MUTSAERTS[2,3], J.C.M. MEIJERS[4,5], N.A. KOOTSTRA[6], P. REISS[7-9], F.W.N.M. WIT[7-9], C.E. TEUNISSEN[10], D. PAJKRT[1]

KEY POINTS

Plasma CRP and sVCAM-1 are elevated in HIV-infected children as compared to healthy controls, and correlate strongly with intrathecal levels

Higher levels of CRP were associated with microstructural white matter injury, and higher levels of sVCAM-1 with poorer visuomotor integration

These results suggest that ongoing inflammation and endothelial activation may play a role cerebral injury despite cART

OBJECTIVE

Children perinatally infected with HIV, despite effective virological suppression with cART, show neuropsychological dysfunctioning with underlying macro- and microstructural brain injury.[1,2] The potential role of (HIV-associated) vascular comorbidity in these deficits is unclear. This study aimed to assess whether systemic and cerebrospinal fluid (CSF) vascular disease biomarkers were associated with cerebral and cognitive deficits in HIV-infected children.

METHODS

This cross-sectional study included cART-treated perinatally infected children aged 8-18 years from the Academic Medical Center in Amsterdam, and age-, sex-, ethnicity- and socio-economic status-matched uninfected controls. We measured markers of inflammation, endothelial activation (with MesoScale Discovery), and coagulation (with enzyme-linked immunosorbent assays) in blood samples from all participants and in CSF from HIV-infected participants.

Using 3-Tesla MRI, we determined gray matter volume, white matter lesion volume, white matter diffusivity (using diffusion tensor imaging)[1], and cortical and subcortical gray matter blood flow (using arterial spin labeling). A neuropsychologist evaluated intelligence, processing speed, attention, visuomotor integration, memory and executive functioning.[2] In the HIV-infected group, we explored associations of all measured markers with HIV-related disease and treatment factors using ordered logistic regression, and with MRI abnormalities and cognitive performance using age- and sex-adjusted linear regression.

RESULTS

Plasma and CSF markers of vascular health

HIV-infected children showed higher systemic levels of CRP and sVCAM-1, as well as strong correlations between blood and CSF levels of CRP, sVCAM-1, and sICAM-1 (Table 1).

Associations with HIV disease and treatment history

Several HIV-related disease factors were associated with vascular markers, most notably higher plasma viral load with higher systemic levels of sVCAM-1, D-dimer, and vWF-antigen and propeptide.

Associations with cerebral injury and cognitive performance

Higher levels of CRP were associated with higher white matter mean diffusivity (blood: coef=2.09; P=.029; CSF: coef=2.27; P=.029). Higher systemic sVCAM-1 was strongly associated with poorer visuomotor integration (coef=-17.6; P=<.001). Vascular markers were not associated with gray matter volume, white matter lesions, cerebral blood flow or other cognitive domains.

CONCLUSIONS

In a well-treated cohort of perinatally HIV-infected children, ongoing inflammation and endothelial activation were indicated by elevated systemic CRP and sVCAM-1, which correlated with CSF levels. These markers were associated with microstructural white matter injury and poorer visuomotor integration, but not with cerebral blood flow or macrostructural cerebral injury. Longitudinal evaluation is warranted to assess whether the presence of inflammation and endothelial activation negatively affects white matter microstructure and cognitive performance over time.

TABLE 1 STUDY PARTICIPANTS

37 healthy controls	36 HIV-infected children
median age of 12.1 years	median age of 13.7 years
49% male	50% male
	25% CDC-C diagnosis
	nadir CD4⁺ T-cell count 445 *10⁶/L (Z-score -0.7)
	86% on cART since median age 2.6 years
	83% virologically surpressed
	CD4⁺ T-cell count 765 *10⁶/L (Z-score -0.1)

	plasma	*plasma*	*P-value[a]*	*CSF[†]*	*P-value[b]*
CRP (mg/l)	0.28 (0.16-0.81)	0.72 (0.30-2.48)	*.004**	.0023 (.0009-.0074)	*<.001**
IL-6 (pg/ml)	0.25 (0.08-0.38)	0.34 (0.08-0.52)	*.33*	0.7 (0.5-0.8)	*.88*
sVCAM-1 (ng/ml)	591 (437-668)	642 (525-838)	*.026**	6.91 (5.58-11.58)	*.005**
sICAM-1 (ng/ml)	438 (390-503)	469 (400-538)	*.26*	2.64 (2.03-3.65)	*.004**
D-dimer (µg/ml)	0.21 (0.16-0.33)	0.27 (0.16-0.46)	*.30*		
F1+2 (pmol/l)	115 (101-151)	128 (108-153)	*.36*		
TAT (µg/ml)	3.5 (3.1-4.2)	3.5 (3-4.3)	*.95*		
vWF-ag (%)	107 (87-138)	110 (86-148)	*.60*		
vWF-pp (%)	101 (89-115)	96 (84-115)	*.65*		

Markers are median (IQR). Abbreviations:Abbreviations: hsCRP=high sensitivity C-reactive protein; IL=interleukin; sVCAM=soluble vascular cell adhesion molecule; sICAM= soluble intercellular cell adhesion molecule; F1+2=prothrombin fragment 1 + 2; TAT=thrombin-antithrombin III complex; vWF (ag)= von Willebrand factor antigen; vWF (pro)= von Willebrand factor (propeptide). Footnotes: [†] Inflammation and endothelial activation data was missing for one HIV-infected participant and coagulation data was missing for another. ‡ data missing for one participant. [a] Group differences in plasma levels (Mann-Whitney-U test); [b] Correlations between blood and CSF levels (Spearman's rank correlation); *P-value <.05;

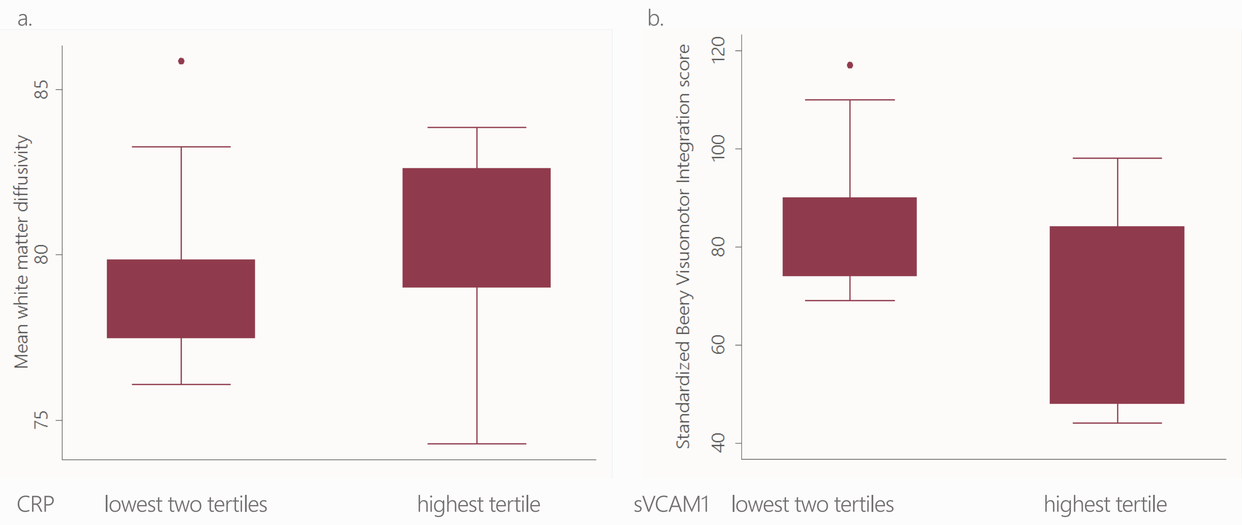

Figure 1. Correlations of inflammatory and endothelial activation markers with cerebral injury and cognitive dysfunction.

a. Higher CRP was associated with mean white matter diffusivity, as measured with diffusion tensor imaging. Increased white matter diffusivity is suggestive of microstructural white matter damage.

b. Higher sVCAM-1 was associated with poorer visuomotor integration, as measured with the Beery visuomotor score.

REFERENCES: [1]Cohen et al, Clin Infect Dis 2015;60(7):1111-1119. [2]Cohen et al, Neurology 2016;86(1):19-27.

AUTHOR AFFILIATIONS: [1]Department of Pediatric Hematology, Immunology and Infectious Diseases, Emma Children's Hospital, Amsterdam [2]Department of Radiology, Academic Medical Center, Amsterdam [3]Cognitive Neurology Research Unit, Sunnybrook Health Sciences Centre, Toronto, Canada [4]Department of Global Health, Academic Medical Center/Amsterdam Institute for Global Health and Development, Amsterdam [5]Department of Internal Medicine, Division of Infectious Diseases, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, Amsterdam [6]HIV Monitoring Foundation, Amsterdam

Presenting author: Marrit van Zanten
Corresponding author: Charlotte Blokhuis (c.blokhuis@amc.nl)
Pediatric Infectious Diseases, Emma Children's Hospital, Amsterdam

NOVICE
Aids Fonds
ViiV Healthcare
Maarten Kapelle Stichting
emma kinderziekenhuis AMC