Systemic inflammation and structural brain changes in perinatally HIV+ adolescents

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INTRODUCTION

Neurocognitive impairments despite ART are well documented in PHIV+

Mechanisms that drive this are not well defined

Systemic inflammation may be one mechanism but this has not been investigated in adolescence when the brain is undergoing rapid development

PHIV+ on ART from CTAAC have impairment in general intellectual functioning, attention, working memory, visual memory, verbal memory, processing speed and executive function when compared to HIV negative controls.

51% of the cohort have a neurocognitive disorder with associated functional impairment

PHIV+ from CTAAC have increased risk of CNS regional WM microstructure alterations, smaller gray matter volumes, reduced cortical surface area and decreased gyrification

Suggesting abnormal neurodevelopment in PHIV+

In the current study we aimed to investigate how neurocognitive and whole brain neurostructural measures were associated with concurrently measured markers of systemic inflammation including hs-CRP and fasting LDL-C within the CTAAC cohort

METHODS

Baseline data were drawn from the Cape Town Adolescent Antiretroviral Cohort (CTAAC). PHIV on ART >6m at public sector facilities completed a comprehensive neurocognitive test battery assessing function in 10 cognitive domains. Diffusion tensor imaging and structural brain magnetic resonance imaging (MRI) was done to determine fractional anisotropy (FA), mean diffusivity (MD), axial diffusion (AD), radial diffusion (RD) gray and white matter volumes, cortical thickness and cortical surface area. In analysis we examined how neurocognitive and neurostructural measures were associated with concurrently measured markers of systemic inflammation including hs-CRP and fasting low density lipoprotein-cholesterol (LDL-C).

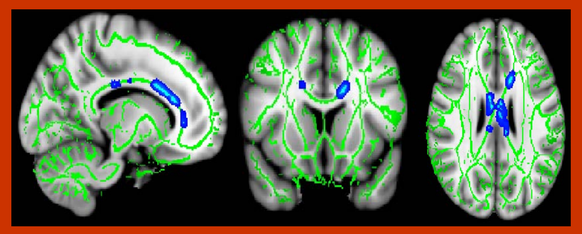
NEUROCOGNITIVE RESULTS

Overall 204 PHIV ages 9-12 years (mean CD4 cell count 953 cells/µL and 85.3% VL<50 copies/mL) and 44 age-matched HIV-controls completed all assessments. PHIV had higher hs-CRP (p<0.001) and LDL (p=0.06) vs controls. Among PHIV, hs-CRP negatively correlated with multiple neurocognitive measures including general intelligence (p=0.005), attention (p=0.015), working memory (p=0.003), visual space acuity (p=0.005), processing speed (p<0.001), and executive function (p=0.002); LDL-C negatively correlated with Language (p=0.048), but positively correlated with attention (p=0.023) and working memory (p=0.024); however none of these correlations were apparent among controls. hs-CRP was highest in PHIV with a major neurocognitive disorder (p=0.004). No differences in LDL-C, total cholesterol and triglycerides across neurocognitive disorders

Variable	PHIV (N = 204)	Controls (N = 44)	P
Age in years: Mean (SD)	10.38 (0.88)	10.38 (1.09)	.99
Gender: Male/Female	100/104	20/24	.67
Ethnicity: Black African/Other	187/17	44/0	.05
Home language: isiXhosa/ Other	182/20	42/2	.26
Education in years: Mean (SD)	3.20 (1.13)	3.39 (1.35)	.34
Repeated grades: YES/NO	121/83	18/26	.02*
Orphanhood[a]	71 (35%)	6 (14%)	.00*
Anthropometry			
Weight in kg	30.79 (7.26)	36.79 (11.26)	.00*
Height in cm	133.82 (7.72)	138.59 (8.76)	.00*
Head circ in cm	52.93 (2.14)	53.61 (3.07)	.08
Tanner's staging			
Breast develop.	1.53 (.74)	1.87 (.61)	.04*
Pubic hair	1.29 (.58)	1.58 (.93)	.05*
Testes growth	1.11 (.34)	1.15 (.37)	.60
Total Cholesterol	4.26(0.89)	3.88(0.72)	.01*
Triglycerides	0.99(0.44)	0.75(0.35)	<.01*
HDL	1.56(0.41)	1.53(0.32)	.63
LDL	2.25(0.76)	2.02(0.61)	.06
hs-CRP	3.90(7.08)	1.14(1.48)	<.01*
ART regimen: First/Second/Third line	163/32/9		
Duration of ART: mean years (SD)	7.18 (2.46)		
Age of initiation: mean years (SD)	3.41 (2.53)		
Viral load median (copies/mL)	0(40)		
CD4 count mean (cells/mm3)	953		

	All subjects (n=236)	HCs only (n=43)	PHIVs only (n=193)	PHIVs without NCD (n=92)	PHIVs with NCD (n=101)
Tcholesterol Attention			.051		.021
Tcholesterol Working memory			.042		.051
Tcholesterol Language				.043	
Tcholesterol Motor coordination					
LDL Attention			.023		.007
LDL Working memory			.024		.019
LDL Language			.048		
LDL Motor coordination					
HDL Verbal memory			.033		
Trig General intelligence					
Trig Motor coordination					.035
Trig Processing speed					
hsCRP General intelligence	.005		.003		.053
hsCRP Attention	.015		.003		
hsCRP Visual spatial acuity	.005		.007		
hsCRP Processing speed	<.001		.001		.056
hsCRP Working memory	.003		.001		
hsCRP Executive function	.002		.001		.032

Whole Brain Means	hs-CRP	TChol	HDL	LDL	Triglycerides
In PHIVs and HCs combined					
GM Volume	.04(.60)	.07(.32)	.10(.14)	.03(.68)	.01(.98)
WM Volume	-.02(.81)	.04(.59)	.09(.19)	.01(.89)	-.03(.64)
Cortical Thickness	.01(.89)	.18(01)**	.15(.02)**	.13(.06)	.02(.73)
Mean FA	-.03(.77)	-.01(.89)	.09(.29)	-.03(.76)	-.09(.26)
Mean MD	.09(.31)	.03(.73)	.02(.79)	.05(.56)	-.01(17)
In HCs					
GM Volume	-.21(.17)	.12(.44)	.26(.09)	.05(.76)	-.19(.20)
WM Volume	-.15(.34)	.03(.87)	.16(32)	.01(.96)	-.25(.11)
Cortical Thickness	-.22(.17)	.01(.93)	.19(.19)	-.08(.59)	-.17(.66)
Mean FA	.19(.40)	.12(58)	-.05(.84)	.11(.62)	.24(.28)
Mean MD	-.26(.25)	09(.34)	.06(.79)	.45(.04)**	.11(.63)
In PHIVs					
GM Volume	.06(.44)	.06(.39)	.07(.34)	.03(.72)	.04(.58)
WM Volume	-.01(.96)	.05(.54)	.08(.29)	.01(.85)	.02(.84)
Cortical Thickness	.02(.76)	.22(.01)**	.15(.05)	.17(.03)**	.04(59)
Mean FA	.00(.99)	.01(.99)	.11(.24)	-.02(.82)	-.09(.27)
Mean MD	.45(.03)**	-.04(.69)	.02(.87)	-.01(.90)	-.17(.06)



NEUROIMAGING RESULTS

Whole brain MD increased with higher hs-CRP values. Higher MD is suggestive of inflammation and myelin loss. Whole brain mean cortical thickness increased with higher levels of LDL-C in PHIV (p=0.03).

CONCLUSIONS

hs-CRP higher in PHIV+ vs controls

hs-CRP negatively correlated with multiple neurocognitive domains in PHIV+; no correlations in controls

hs-CRP was highest amongst PHIV+ with a Major NCD

Whole brain MD increased with higher hs-CRP values. Higher MD is suggestive of inflammation and myelin loss

Relationship of LDL-C with neurocognitive function and brain structure not clear

While further investigation including long-term follow-up is required, this provides novel evidence that inflammatory mechanisms may drive persistent neurological impairment in PHIV+