ELEVATED SYSTEMIC IL-15, IFN-γ, IP-10, AND MCP-1 DO NOT CORRELATE WITH INTRATHECAL INFLAMMATION IN CART-TREATED PERINATALLY HIV-INFECTED CHILDREN

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KEY POINTS

IL-15, IFNγ, IP-10 and MCP-1 were mildly elevated in clinically stable HIV-infected children

Systemic inflammation/immune activation may not be a reliable proxy for intrathecal inflammation/ immune activation in cART-treated children

Poor virological control or low CD4+ T-cell counts were not associated with elevated inflammation/ immune activation in children on cART

OBJECTIVE

The contribution of inflammation to cognitive defects and cerebral injury in cART-treated perinatally HIV-infected children is largely unknown. In adults, systemic and intrathecal inflammatory/immune activation markers such as MCP-1, IP-10 and sCD14 have been associated with cerebral injury[1] and cognitive impairment[2,3]. We aim to assess the relationship between inflammation/immune activation and cerebral injury in cART-treated perinatally HIV-infected children. In a first analysis we focus on characterizing systemic and intrathecal inflammatory/immune activation markers, and potential associations with HIV-related disease and treatment factors.

METHODS

This cross-sectional study included perinatally HIV-infected children between 8-18 years from Amsterdam and age-, sex-, ethnicity-, and socio-economically matched controls (Table 1). Using MesoScale Discovery, we analysed inflammatory cytokines, chemoattractants and monocyte activation markers in plasma samples of all participants, and cerebrospinal fluid (CSF) only of HIV-infected participants. Potential associations between HIV-related disease and treatment factors and inflammatory/immune activation markers were explored using ordered logistic regression.

RESULTS

Plasma inflammation/immune activation

HIV-infected children showed higher plasma levels of IL-15, IFNγ, IP-10, and MCP-1 as compared to controls (Table 1).

CSF inflammation/immune activation

Plasma and CSF levels of inflammatory/immune activation markers were not - or even inversely (IL-1b and IL-8) - correlated in HIV-infected children (Table 1).

Correlations with HIV disease and treatment history

- Participants with a shorter lifetime duration of $CD4^+$ T-cell counts < $500*10^6$ (log months) had higher plasma IFNγ (coef=-0.99, P-value=.019).
- A higher CD4+ T-cell count Z-score at study inclusion (coef=1.93; P-value=.029) and older age at cART initiation (coef=-0.22; P-value=.037) were associated with higher plasma MCP-1.
- A Centers for Disease Control and Prevention stage C diagnosis was associated with higher CSF IL-15 (coef=3.18; P-value=.041).
- No associations were found between any of the markers and detectable systemic or intrathecal viral load.

CONCLUSIONS

Inflammation-associated biomarkers IL-15, IFNγ, IP-10 and MCP-1 were mildly elevated in HIV-infected children as compared to healthy controls. Increased plasma levels did not correlate with increased intrathecal levels, and may thus not accurately reflect inflammation/immune activation within the central nervous system.

As inadequate viral suppression or low $CD4^+$ T-cell counts were not associated with increased systemic inflammation/immune activation, other mechanisms may regulate inflammation when stable on treatment. The association between older age at cART initiation and higher MCP-1 could imply that early cART initiation may reduce systemic inflammation.

In further analyses, we aim to evaluate how these biomarkers relate to macro- and microstructural cerebral injury and cognitive impairment in pediatric HIV.

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 $*10^6$/L (Z-score -0.7)
	86% on cART since median age 2.6 years
	83% virologically surpressed
	$CD4^+$ T-cell count 765 $*10^6$/L (Z-score -0.1)

	plasma	*plasma*	*P-value[a]*	*CSF[†]*	*P-value[b]*
IL-1α	0.6 (0.2.2.0)	04 (0.1-1.5)	*.27*	1.3 (0.9-2.0)	*.48*
IL-1β	0.02 (0.02-0.29)	0.02 (0.02-0.07)	*.64*	0.2 (0.1-0.5)	*.008**
IL-6	0.3 (0.1-0.4)	0.3 (0.1-0.5)	*.33*	0.7 (0.5-0.8)	*.87*
IL-8	2.3 (1.5-3.3)	2.2 (1.4-3.2)	*.65*	23.7 (18.8-27.8)	*.029**
IL-12p40	150 (123-203)	180 (101-232)	*.78*	3.1 (2.3-20.9)	*.94*
IL-15	1.1 (0.9-1.6)	1.6 (1.1-2.0)	*.014**	1.0 (0.9-1.7)	*.93*
TNFα	2.0 (1.7-2.4)	2.3 (1.8-3.3)	*.087*	0.2 (0.1-0.3)	*.29*
IFNγ	5.7 (4.2-8.7)	9.4 (6.8-14.3)	*.003**	2.6 (1.9-4.2)	*.35*
IP-10	250 (169-314)	348 (239-615)	*.002**	223 (199-275)	*.87*
MCP-1	72.4 (57.1-90.1)	97.5 (76.9-123.3)	*<.001**	276 (223-352)	*.88*
MIP-1α	2.4 (2.4-13.1)	2.4 (2.4-14.4)	*.26*	11.1 (8.8-13.9)	*.12*
MIP-1β	49.4 (40.6-70.6)	49.8 (37.5-77.1)	*.66*	11.6 (9.3-19.1)	*.06*
sCD14	1861 (1131-2484)	1861 (1448-2583)	*.30*	40.2 (25.0-72-1)	*.31*
sCD163	206 (171-276)	216 (150-293)	*.97*	12.3 (8.6-19.1)	*.98*

Markers are median (IQR) in pg/ml. Abbreviations: IL=interleukin; TNF=tumor necrosis factor; IFN=interferon; IP=interferon-gamma-inducible protein; MCP=monocyte chemoattractant protein; MIP=macrophage inflammatory protein; sCD14 and sCD163=soluble cluster of differentiation 14 and 163.

[†] sCD14 and sCD163: 26 samples; other biomarkers: 24 samples. [a] Group differences in plasma levels (Mann-Whitney-U test); [b] Correlations between blood and CSF levels (Spearman's rank correlation); * P-value <0.05

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