Biomarkers of Cognitive Decline in Perinatally-Infected Children with HIV

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Background

Cognitive impairment is common in children with perinatally-acquired HIV (PHIV), but identifying children at high risk of cognitive decline has remained challenging. A combination of biomarkers and clinical characteristics may allow identification of children at high risk of developing cognitive impairment.

Methods

- Data and plasma samples were obtained from PHIV youth on cART ages 6-16 participating in IMPAACT 219C.
- 13 biomarkers of immune activation and inflammation were measured in plasma using ELISA or multiplex assays at 2 timepoints spaced approximately 3 years appart.
- PHIV youth with neurocognitive decline (defined as sustained drop in full scale IQ ≥ 15 points during study follow-up) were compared to age-matched PHIV youth without decline (n=65 per group) in a case-control study.
- Factor analysis was utilized to derive a risk score utilizing a combination of clinical variables and biomarkers and ROC curve analysis was utilized

Results

- In the univariate analysis, cases with cognitive decline had significantly higher levels of interferon-gamma, TNF-alpha and IL8 at time 1 and higher levels of CRP, TNFR1,and sCD163 at time 2 than did controls.
- Cases with cognitive decline had significantly greater increases in CD40 ligand, CRP, and sCD14 over time than did controls without decline.
- A Risk Score utilizing biomarkers and clinical characteristics had excellent performance characteristics for prediction of decline (AUC 0.81)

Subject Characteristics

Variable	Controls (n=65)	Cases (n=65)	P-Value
Age at timepoint 1	9.7 (7-12)	9.2 (8-11)	0.8
Age at timepoint 2	12.2 (11-14)	12.2 (11-13)	1
Black race	27 (42%)	29 (45%)	0.5
Hispanic ethnicity	12 (18%)	28 (43%)	**0.02***
Male Sex	29 (44%)	29 (44%)	1
Born in U.S.	60 (93%)	52 (80%)	**0.03***
Age at cART initiation	6.8 (4.9-9.8)	7.3 (5-9.4)	0.66
Pre-cART viral load	4591 (4299-13,000)	7175 (655-46268)	0.7
Viral load time 1	400 (50-6340)	400 (239-6409)	0.5
Viral load time 2	400 (50-1757)	1027 (400-10,033)	**0.006***
CD4 timepoint 1	950 (572-1180)	737 (496-1052)	0.86
CD4 timepoint 2	726 (515-1022)	655 (439-757)	**0.03***
Adherence time 1	100% (100-100)	100 (86-100)	**0.002***

Variables are reported as median and interquartile range or n (%). Variables with p values <0.05 are in bold and marked with *

Biomarkers in cases vs. controls

Analyte	Time 1		Time 2		Change over time	
	Beta	P-value	Beta	P-value	Beta	P value
hsCRP	-0.68	0.34	↑**.59**	**0.05***	↑**5.3**	**0.04***
Ifn-gamma	↑**0.47**	**0.003***	-0.017	0.88	1.6	0.54
TNF-alpha	↑**0.12**	**0.04***	.04	0.36	-1.03	0.19
TNFR1	0.07	0.45	↑**0.14**	**0.009***	439	0.21
TNFR2	0.13	0.39	0.15	0.09	60	0.89
sCD14	-0.22	0.06	0.07	0.36	↑**444920**	**0.05***
sCD163	0.13	0.59	↑**0.17**	**0.02***	-33446	0.82
IL1B	0.07	0.39	-.09	0.24	-.29	0.72
IL6	0.02	0.83	.07	0.44	.39	0.53
Il8	↑**0.38**	**0.01***	-0.03	0.88	-45	0.10
Il10	↓***-0.28**	**0.002***	0.09	0.24	-1.29	0.25
sCD40L	-0.15	0.43	.22	0.07	↑**546**	**0.04***

Variables with p-values <0.05 are listed in bold and marked with *

Univariate association between variables and cognitive decline

Variable	Odds Ratio	P-value	R^2
CRP (time 2)	2.5 (1.2-5.2)	**0.01***	0.07
TNFR1 (time 2)	4.0 (1.3-12.0)	**0.01***	0.08
TNFR2 (time 2)	1.8 (0.9-3.7)	0.09	0.03
sCD163 (time 2)	2.3 (1.1-4.6)	**0.02***	0.06
sCD14 (time 2)	1.6 (0.73-3.8)	0.23	0.02
sCD40L (time 2)	2.3 (1.1-4.6)	**0.02***	0.06
Biomarker Risk Score[1]	2 (1.4-2.8)	**<0.001***	0.34
Detectable viral load	2.6 (1.1-5.5)	**0.02***	0.07
CD4 count <200	4 (0.9- 18.9)	0.08	0.04
History of CDC class C diagnosis	1.7 (0.67-4.4)	0.26	0.02
Hispanic ethnicity	3.0 (1.3-6.7)	**0.007***	0.09
Born outside U.S.	3.3 (1.1-10.0)	**0.04***	0.06
Caregiver education < 12 years	3 (1.2-7.6)	**0.02***	0.07
Clinical Risk Score[2]	1.9 (1.3-2.6)	**0.001***	0.19

P values <0.05 are in bold and marked with a *. [1]The biomarker risk score was generated using a combination of listed biomarkers weighted based on factor analytic loading. Clinical risk score was generated using a combination of all listed clinical variables weighted using Beta coefficients from a multivariable conditional logistic regression model.

Prediction of decline combining biomarkers and clinical variables

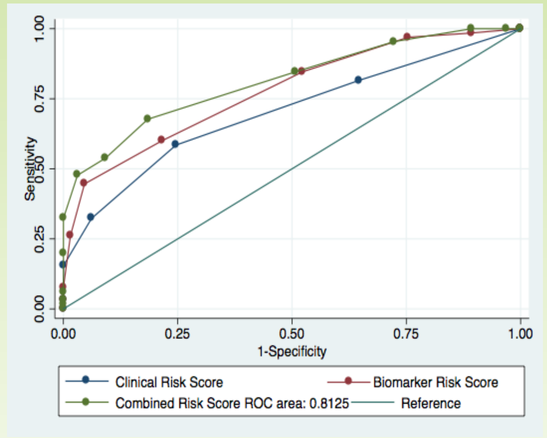

Figure 1: ROC curves comparing biomarker risk score, clinical risk score, and a combined score utilizing both biomarkers and clinical characteristics. AUC was significantly improved for combined score (AUC 0.81 vs. 0.77 vs. 0.70, p<0.001)

CONCLUSION

- These results show a significant association between inflammatory biomarkers and cognitive decline in children with HIV.
- Utilizing clinical characteristics and biomarkers may allow identification of children with HIV at high risk of decline
- Further studies are necessary to confirm these results in a prospective cohort
- Interventions to prevent cognitive impairment could utilize this risk score to target subjects at highest risk of decline.

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