Hepcidin Modifies the Effects of Age and Erythrocyte Indices on Cognitive Function in People with HIV

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BACKGROUND

- Cognitive impairment (CI) in people with HIV (PWH) is associated with abnormal erythrocyte indices, possibly due to inflammation, iron dysmetabolism, aging, and other factors. Mean Corpuscular Volume (MCV, a measure of erythrocyte size), and Mean Corpuscular Hemoglobin (MCH, a measure of hemoglobinization) are erythrocyte indices that reflect changes in iron homeostasis.
- Erythropoiesis requires bioavailable iron, regulated by a complex system of peptide hormones, including the acute-phase peptide, hepcidin.
- **Hypotheses**: Plasma hepcidin levels in PWH modify the impact of age and erythrocyte indices on cognition.

METHODS

- Plasma hepcidin and erythrocyte indices were measured with commercial assays in 88 virally suppressed PWH (viral load < 200 copies/mL) who were taking antiretroviral therapy (ART).
- All participants had comprehensive cognitive testing, and their performance was summarized by T-score values.
- Anemia was defined as hemoglobin concentrations <13.5 g/dL in males and <12 g/dL in non-pregnant females.
- Depressive symptoms were assessed by the Beck Depression Inventory-II.
- Multivariable regression analysis of cognitive performance was performed using the Akaike Information Criterion and backward selection adjusting for sex, race, ethnicity, nadir and CD4+ T-cell count, and ZDV use.

Variable	Hepcidin Undetectable (n = 46)	Hepcidin Detectable (n = 42)
Age (years)	43.5 (11)	44.7 (10.7)
Education (years)*	13.9 (2.2)	13.2 (2.8)
Sex: n (%) female	9 (19.6)	5 (11.9)
Race: n (%) Black	12 (26.1)	7 (16.7)
Ethnicity: n (%) Hispanic	5 (10.8)	12 (28.5)
Taking ART: n (%)	46 (100)	42 (100)
Plasma HIV RNA < 200 c/mL: N(%)	46 (100)	42 (100)
Current CD_4: median (IQR) cells/μL	510 (276.5-793)	488 (192.5 - 739)
Nadir CD_4: median (IQR) cells/μL	152 (31.5-301)	132 (21.5 - 259)
Anemia: n (%)	19 (21.5)	22 (25)

Table 1: Participant Demographic and Disease Characteristics

Hepcidin, a regulator of iron homeostasis, significantly influenced the association between **neurocognition** and the erythrocyte indices **MCV**, **MCH,** and **age** in PWH.

RESULTS

- The mean age of participants was 44 years, most were white (52.3%), males (84.1%), and not anemic (53.5%). The median nadir and current CD4+ T-cell count were 150 and 493 cells/μL, while 67% had an AIDS diagnosis.
- Hepcidin was detectable (>1.0 ng/mL) in 42 (47.7%). In a multivariable analysis, hepcidin detectability interacted with age (p =0.007), and MCV (p =0.019), with a trend for MCH (p=0.082) in relation to the global T-score.
- Analyses stratified by hepcidin detectability: Poorer cognition (lower global T-scores) was associated with older age (p=0.001), and higher MCV (p=0.004) but only when hepcidin was undetectable.
- After multivariate analysis, we found that Interactions between anemia, and RBC indices, as regards global T-scores significant for anemia-MCV (p=0.0119) and anemia-MCH (p=0.0127). Amongst the anemic, poorer cognition was associated with higher MCV (p=0.002) and higher MCH (p=0.0026).
- Similar effects of hepcidin and anemia were not present for depressive symptoms.

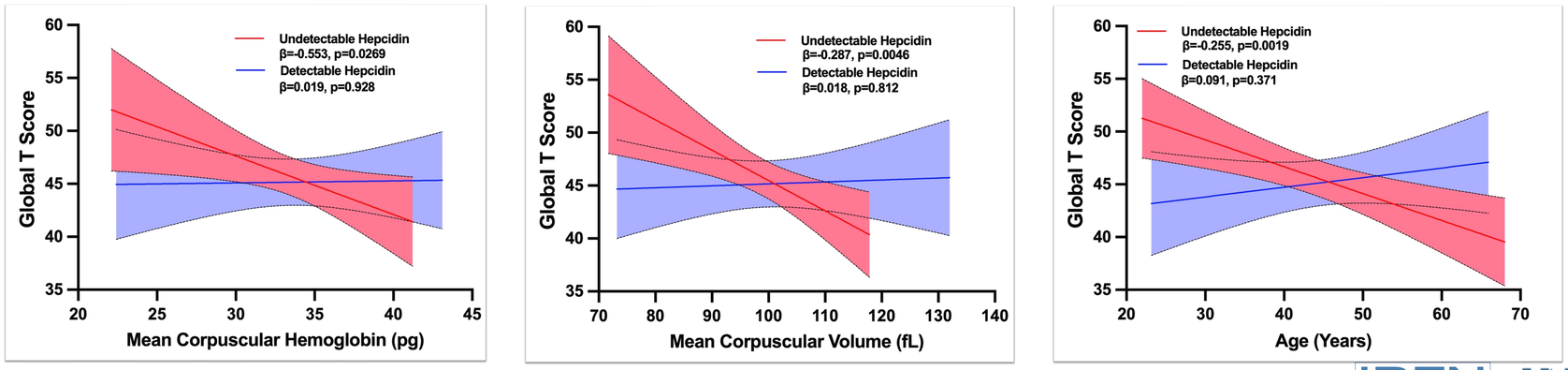


Figure: Hepcidin modifies the relationship between global T-score, erythrocyte indices, and age in PWH.

CONCLUSIONS

- Iron-related factors (hepcidin, MCH) and other variables (age, higher MCV) collectively influence neurocognitive health.
- Hepcidin is a potential effect modifier in the associations between age, red cell indices, and neurocognitive function in PWH.
- Global research into how differences in diet, genetics, and access to healthcare impact iron regulation and cognition in PWH is crucial.
- Our study limitations include a small sample size and a lack of inflammatory biomarkers.
- Longitudinal studies with more women are needed to better delineate relationships between hepcidin levels, erythrocyte indices, and neurocognitive performance.

ADDITIONAL KEY INFORMATION

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References:

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