Plasma Neopterin as a Potential Biomarker for Neurocognitive Impairment in Aging People with HIV

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BACKGROUND

- Surrogate markers of neurocognitive impairment (NCI) are needed in people aging with HIV.
- Neopterin is a well-known marker of immune activation and inflammation.
- In HIV infection, Neopterin in CSF has been linked to NCI, but in plasma its potential usefulness remains unclear.
- We assessed the levels of plasma Neopterin comparing three screening tools for NCI in people with HIV.

METHODS

Study Design and Population

The ALI Study (*Exploring Suggestive Symptoms of Preclinical ALzheimer's Disease in People with HIV*) was designed to compare existence of pre-clinical symptoms of Alzheimer's Disease (AD) in people aged ≥50 years with and without HIV. The selection of the participants was based on a prevalence analysis considering the total number of HIV population attended in the Infectious Diseases Department of Germans Trias i Pujol Hospital, Badalona, Catalonia, Spain. Stratification was applied in terms of sex and age. The HIV group were on ART and had indetectable plasma viral load (<20 cop/ml, <6 months). Candidates were proposed to participate and accepted voluntarily. A total of 100 participants were recruited in the HIV group. The control group was recruited from the primary care, were matched to age, sex, and education level, and were confirmed to have a negative HIV test. A total of 50 people were recruited. All participants were informed about the objectives and procedures of the study and signed written consent. The study was approved by the local IRB (*Germans Trias: PI-21-003*).

Variables and Instruments

Demographic, clinical, functional, and neurocognitive variables were collected. With regard to neurocognitive variables, three screening tools were applied: Mini-Mental State Examination (MMSE), FACEmemory®, and NEU Screen. A peripheral blood sample was collected and plasma Neopterin levels were measured by competitive ELISA.

Data Analyses

Descriptive tests were applied for the total sample and in each group. For categorical variables, comparisons between groups were performed using Chi-Square test; for numerical variables, Mann-Whitney U test was used. For Neopterin data analyses, comparisons were applied considering NCI classification according with the three screening tools.

Our results strengthen the role of **NEU Screen** as a valuable tool screening for neurocognitive impairment in people aging with HIV. Additionally, we offer relevant outcomes underscoring the usefulness of **Neopterin** as a plasma biomarker detecting neurocognitive decline in this population.

RESULTS (I)

Most participants were men (74%), with a median age of 58 (IQR: 54 - 64) years, and 12 (8 - 15) years of formal education. Compared to the control group, people with HIV (PWH) had significantly higher rates of polypharmacy (29% vs 10%; *p*=0.009), substance use in the last month (28% vs 2%; *p*<0.001), and a history of substance use disorder (48% vs 18%; *p*<0.001). Characteristics of the study groups are shown in ***Table 1***.

Table 1. *Characteristics of the study groups.*

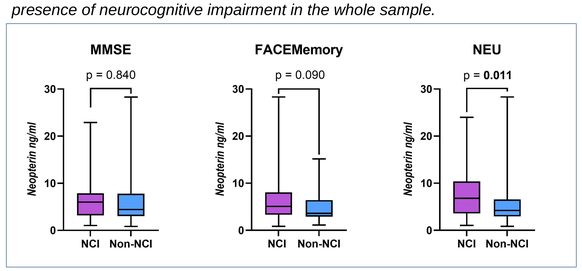
	HIV+ (n=100)	HIV- (n=50)	*p* value
Women, n (%)	26 (26)	15 (30)	0.640
Age, years	58 (55 - 64)	58 (53 - 65)	0.593
Education, years	12 (8 - 14)	12 (9 - 15)	0.474
Years since HIV diagnosis	28 (18 - 31)	-	
CD4+ cell count	653 (481 - 871)	-	
CD4+ nadir	228 (96 - 331)	-	
CNS comorbidities, n (%)	21 (21)	6 (12)	0.176
Relatives with dementia, n (%)	24 (24)	19 (38)	0.074
Polypharmacy, n (%)	29 (29)	5 (10)	**0.009**
Substance use last month, n (%)	28 (28)	1 (2)	**<0.001**
Active alcohol use disorder, n (%)	7 (7)	1 (2)	0.199
Past substance disorder, n (%)	48 (48)	9 (18)	**<0.001**
Depressive symptoms	3 (1 - 5)	3 (1 - 5.5)	0.717
Anxiety symptoms	6 (3 - 9)	5 (4 - 8)	0.706
Daily living impairment	12 (12)	5 (10)	0.716

Table 2. *Neurocognitive and Neopterin outcomes.*

	HIV+ (n=100)	HIV- (n=50)	*p* value
Cognitive reserve	13 (9 - 17)	14 (11 - 17)	0.265
Positive EACS cognitive screening	19 (19)	16 (32)	0.088
Positive MMSE	14 (14)	3 (6)	0.145
Positive FACEmemory®	61 (70)	28 (56)	0.095
Positive NEU Screen	36 (37)	8 (16)	**0.009**
Neopterin levels	6.2 (3.3 - 9.1)	3.5 (3 - 4.8)	**0.001**

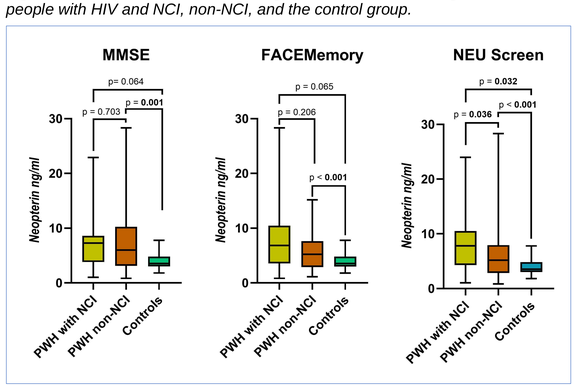
Values in both tables expressed as median (interquartile range), except when indicated otherwise. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Shi-square test. Statistical significance was set at p<0.05. Bold values denote statistical significance.
Depressive and anxiety symptoms assessed by Hospital Anxiety and Depression Scale (HADS); Cognitive reserve by Cognitive Reserve Questionnaire (CRC); Instrumental Activities of Daily Living by Instrumental Activities of Daily Living (IADL) Questionnaire.
Abbreviations: CG, Control Group; CNS, Central Nervous System; EACS, European AIDS Clinical Society; MMSE, Mini-Mental State Examination; PWH, People with HIV.

Figure 1. *Neopterin levels according to the three screening methods and presence of neurocognitive impairment in the whole sample.*



Box plots depicting neopterin levels in participants with neurocognitive impairment (NCI) and without (Non-NCI), as determined by the three screening tools (MMSE, FACEmemory, NEU). Data represent the entire sample, regardless of serostatus. Boxes show the median and interquartile range (IQR), and whiskers extend to the minimum and maximum values observed. P values from the Mann-Whitney U test are displayed above each plot.

Figure 2. *Neopterin levels according to the three screening methods and people with HIV and NCI, non-NCI, and the control group.*



Box plots of neopterin levels among three groups: people with HIV (PWH) and neurocognitive impairment (NCI), PWH without NCI, and HIV-negative controls, as assessed by the three screening tools (MMSE, FACEmemory, and NEU Screen). Boxes show the median and interquartile range (IQR), and whiskers extend to the minimum and maximum values. P values from Mann-Whitney U comparisons are displayed above the brackets.

RESULTS (II)

Positive screening for NCI was more prevalent in PWH than in controls according to the three screening methods, reaching statistical significance only with the NEU Screen: MMSE: 14% vs 6%, *p*=0.145; FACEmemory: 70% vs 56%, *p*=0.095; and NEU Screen: 37% vs 16%, *p*=0.009 (***Table 2***). Neopterin levels were higher in PWH compared to controls: 6.21 ng/ml (IQR: 3.26 - 9.14) vs 3.54 ng/ml (IQR: 2.99 - 4.82), p=0.001. Considering the three screenings, Neopterin levels were always higher when positive NCI was detected, with significance only when using the NEU Screen classification (***Figure 1***). When NEU Screen was applied, Neopterin levels also allowed to discriminate difference between PWH with suspected NCI and PWH without suspected NCI (***Figure 2***).

CONCLUSIONS

The higher levels of plasma Neopterin observed in aging PWH compared to HIV-negative individuals suggest persistent immune activation despite effective ART. Elevated Neopterin levels were significantly associated with suspected NCI as measured by the NEU Screen. These results reinforce the NEU Screen as a useful NCI screening test in HIV infection, and, additionally, underscore the potential utility of Neopterin as a plasma biomarker for cognitive decline in aging PWH.

COLLABORATING CENTERS

- Fight Infectious Foundation – Germans Trias i Pujol Hospital, Badalona, Catalonia, Spain
- IrsiCaixa Institute, Badalona, Catalonia, Spain
- Ace Alzheimer Center Barcelona, Barcelona, Catalonia, Spain

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