Assessment of Plasma Neurofilament Light as a Biomarker of Neuronal Injury in Young Adults with Perinatal HIV Infection

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Abstract

Background: Higher plasma concentration of neurofilament light (pNfL) is associated with neurodegeneration. However, to our knowledge, up to now, there are no data in HIV patients with infection due to vertical transmission. This is the first study to report pNfL in a cohort of HIV perinatally infected (PHIV) young adults compared with non-HIV (HIV-) controls.

Methods: Thirty-three PHIV patients and 25 age-matched HIV- were recruited to this cross-sectional study. Plasma NfL concentrations were compared between both groups. In a subgroup of 48 participants (25 PHIV patients and 23 HIV-), brain volumes through magnetic resonance imaging (MRI) and neuropsychological testing (NT), were also conducted and compared with pNfL values.

Plasma NfL concentration was measured using Single Molecule Array (Simoa) immunoassay.

NT included fluid intelligence and processing speed through the WAIS-IV Coding subtest, and the Stroop Test.

Results

Fifty-eight participants were included, median age 20.7 years [IQR 17.8-23.4]. 100% of the patients were under antiretroviral treatment (cART) and 85% had viral load <50 copies/ml.

Although no statistically significant differences were found between patients and controls regarding pNfL concentration, there was a trend towards higher levels in patients with viral load >50 copies/ml.

With regard to brain volumes and NT, in the PHIV group, lower white matter volumes and lower score in the coding subtest were associated with higher pNfL values.

Conclusions

Most PHIV adolescents under cART have similar levels of pNfL than HIV-. As reported in adults, those with HIV-RNA >50 copies/ml showed higher values and lower white matter volumes that may imply an ongoing CNS injury. Plasma NfL could be a feasible biomarker of CNS injury in PHIV patients with unsuppressed viral load.

Background

The incidence of HIV encephalopathy and severe neurological complications has been significantly reduced in perinatally HIV-infected patient since the introduction of combined antiretroviral therapy¹. Nevertheless, in the PHIV population, CNS invasion of HIV occurs within the first 3 weeks of life, with a subsequent immune activation throughout the primary infection. This is among the most important reasons why research concerning the detection of persistent neurologic problems is essential². This

research could explain why less severe cognitive impairment often could persists in this population, especially in children who did not start treatment in early life³.

To better understand how the development of brain injury and intrathecal immune activation and inflammation occur, several CSF biomarkers have been investigated, with CSF neurofilament light (NfL) being the most useful biomarker for the study of HIV-induced neuroaxonal injury⁴. This major structural component of myelinated axons is essential to maintain axonal calibre and to facilitate effective nerve conduction⁵. It is a sensitive, but disease-unspecific, biomarker for neuronal degeneration or acute neuronal damage⁶.

Several studies performed in HIV-infected adults have shown increased CSF NfL levels in patients with HIV associated dementia but also in neuroasymptomatic subjects with low CD4 + T-cell counts⁵⁻⁷. Meanwhile, treated and virologically suppressed people living with HIV have lower CSF NfL levels, but this is still slightly higher than HIV-negative individuals⁵.

Measuring CSF NfL uses the invasive procedure of lumbar puncture, so its use is limited. Therefore, a new technique has been developed using ultrasensitive (Simoa) immunoassay for measuring NfL in blood samples⁸. Results derived using this new method show that plasma NfL correlates strongly with CSF NfL levels at all stages of HIV infection⁸.

To our knowledge, no study of plasma or CSF NfL has been performed in the perinatally HIV-infected population.

It is worth stating, that in recent years, several neuroimaging studies have been performed in PHIV children and young adults demonstrating that, even in the cART era, there are alterations and lower volumes in brain structure⁹. As NfL CSF levels reflect leakage from injured or degenerating neurons, it correlates with white matter lesions and other injuries to subcortical brain regions¹⁰. To date, there are no studies correlating white matter brain volumes and pNfL values in perinatally HIV-infected patients.

Therefore, the current study aimed to investigate, firstly, the pNfL levels in a group of PHIV population and compared them with a group of HIV-negative controls participating in the NeuroCoRISpe study. Secondly, a sub-study was performed to explore possible correlations between pNfL concentration and white matter volumes and processing speed performance in a group of participants.

Methods

Population and Study Design

A multicentre cross-sectional study was carried out from 2016 to 2018 in a cohort of vertically HIV-infected adolescents and young adults followed at five public hospitals participating in the Madrid Cohort

of HIV-Infected Children and Adolescents and in the Cohort of Spanish Pediatric HIV Network (CoRISpe)
11.

The HIV- were selected from voluntary recruitment through advertising.

Thirty-three PHIV patients and 25 HIV- controls matched by age were recruited.

For the study, all participants met the following inclusion criteria: (1) age 15 to 25 years old, (2) absence of neurological or psychiatric disorder other than history of older HIV encephalopathy, (3) HIV participants should be under cART treatment.

Participants with current brain infection, neurological or psychiatric disorder, those who referred history of drug or alcohol abuse, or had any congenital abnormality, were excluded.

The Institutional Review Boards (IRBs) of each research centre approved the study and written informed consent was obtained from all participants. Where participants were underage, an assent form was signed by themselves, with legal guardians providing the informed consent in accordance with the Helsinki Declaration.

HIV-related measures

In relation to the control of the infection the next parameters were collected: CDC classification, encephalopathy, suppressed viral load (defined as plasma HIV-RNA < 50 copies/ml), time of suppressed viral load, viral load in detectable patients, total numbers, and percentages of CD4 nadir, and current CD4, CD4 / CD8 ratio, cART history and adherence to treatment. These data were collected from clinical charts and the CoRISpe database.

Plasma NfL measurements

Whole blood was collected in EDTA tubes which were sent to the Spanish HIV HGM BioBank for centrifugation (2000 g) and aliquoted into cryo tubes in 1 mL portions and stored at – 80° for subsequent analysis¹². Plasma NfL concentration was measured using a sensitive in-house sandwich immunoassay on the (Simoa) HD-1 Analyzer (Quanterix, Billerica, MA), as previously described in detail⁸.

Neuropsychological and neuroimaging sub-study

A subgroup of 48 participants (25 PHIV +, 23 HIV-) with no differences in sex, age, level of education and socioeconomic status between groups, underwent NT testing and MRI scan. These subjects participated previously in a neurocognitive and neuroimaging study (Ruiz-Saez et al, 2021)¹³ and whole blood was collected at the same time and stored at the HIV HGM Biobank for subsequent pNfL analysis.

The NT included fluid intelligence (FI) by the Kaufman Brief Intelligence Test¹⁴ (K-BIT; Kaufman & Kaufman, 2000), and processing speed measured through two tests, the Digit Symbol-Coding subtest of

the Wechsler Adult Intelligence Scale- 4th edition¹⁵ (WAIS-IV, Weschler, 2012), and the first trial of the Stroop Test¹⁶ (Golden, 2001).

In this study, we focused on fluid intelligence to make sure abstract reasoning and problem solving in novel situations independently of experience was average in both groups. Processing speed was also evaluated, because is one of the main cognitive deficits in HIV patients¹⁷. Scores on all neuropsychological tests were converted into a Z-score relative to HCs. Scores on the Digit Symbol-Coding and Stroop-Card 1 were averaged into one PS composite Z-score.

MRI data acquisition

Different MRI scanner systems were used at each hospital study site. For specific details of the acquisition parameters see Supplementary material.

Image quality was assessed in two independent processes. Radiologist checked for the presence of any brain pathology, such as tumour, cyst, or any other lesion.

In addition, image quality and processing experts checked for motion artefacts, low contrasts, incomplete whole brain coverage, low SNR and low resolution. In a further analysis, all the acquisitions were correlated to determine the homogeneity of the image sample.

Image processing

The standard processing pipeline for volume based morphometry provided by The Computational Anatomy Toolbox (CAT12, <http://dbm.neuro.uni-jena.de/cat/> version 1492), as an extension of SPM (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/> version 7487), was used for tissue segmentation and the extraction of tissue volumes. To measure regional brain volumes, native segmented images were parceled in regions of interest (ROI) according to the Hammers atlas¹⁸⁻¹⁹ (Hammers et al. 2003; Gousias et al. 2008) and tissue volumes (mm³) were estimated for each ROI and normalized by the total intracranial volume for each subject.

Statistical analysis

Categorical variables were summarized by using counts and proportions and continuous variables employing medians and interquartile ranges (IQR) or means and standard deviations (SD). Comparisons between patients and controls (NfL, age, Fluid Intelligence, Stroop, Coding and Composite z-score) were performed with the Student t test or the Mann–Whitney *U* test, if the variables did not follow a normal distribution. Comparisons between categorical variables were assessed using the Chi-square or the Fisher test. In the case of patients with and without undetectable viral load and controls, variables were analyzed with the Kruskal-Wallis test. Regarding the PHIV group, univariate analysis was performed to study associations between HIV variables and NfL. Spearman's correlation test was used to assess association pNfL concentrations and white matter volumes. P values less than 0.05 were considered statistically significant. All analyses were performed using SPSS software ver. 22.0 (IBM, Armonk, NY, USA). Figure 2 was made using Stata Version 12 (STATA Corp, Texas, USA).

Results

Thirty-three young adults with perinatal HIV infection and 25 HIV-negative individuals were included.

In the PHIV group, 54% were women and 73% were Caucasians. Median age was 20.7 years (IQR 17.8–23.4). In the HIV-negative group, median age was 21.3 years (IQR 19.7–23.1) and 60% were women. There were no significant differences between the two groups regarding these characteristics ($p > 0.05$).

Regarding the PHIV group, 42% had a history of previous AIDS-defining diagnoses (21% with old and stable encephalopathy). At assessment, 100% were under cART for a median time of 16.42 years (IQR 12.99–18.70), and 85% had suppressed viral load (HIV RNA < 50 copies/ml); Only five patients had HIV-RNA > 50 copies/ml with a median of 69900 copies/ml (IQR 36774–267541). Those five patients had detectable viral load for a median of 5.75 years (IQR 5.03–16.75). Median CD4 was 738 cells/mm³ (IQR 578–978) and median CD4 nadir 274 (IQR 104–382). (Table 1).

Table 1

Clinical measures in 33 PHIV patients (n (%) or median [IQR])

Age at HIV diagnosis (years)	0.50 [0.24-4.08]
CDC Stage C3	14 (42.4%)
Encephalopathy	7 (21.2%)
NADIR CD4 (cells/mm3)	274 [124-376]
NADIR CD4 (%)	12 [6-17]
CD4 count (cells/mm3)	718 [490-771]
CD4 count (%)	36 [32-39]
CD4/CD8	1.03 [0.80-1.31]
Age at treatment onset (years)	1.33 [0.44-4.56]
Age at onset on cART (years)	4.28 [1.03-6.66]
Total time of treatment with cART (years)	16.42 [12.99-18.70]
Patients with uVL	28 (85%)
Time with uVL (years)	9.97 [6.92-13,48]
VL in detectable patients (cop/ml) (N = 5)	69900 [36774-267541]

No statistically significant differences were found between patients and controls regarding pNfL concentrations, but higher levels of pNfL were found in patients with increased viral load compared with undetectable patients and controls with a media pNfL of 9.19 pg/ml (SD 5.18) in patients with detectable viral load vs 6.6 pg/ml (SD 4.15) in undetectable patients and 5.29 pg/ml (SD 1.75) in the control group ($p = 0.059$) (Fig. 1).

Furthermore, no correlations were found between pNfL levels and viral load, time to diagnosis, time on cART, CDC stage or presence of encephalopathy ($p > 0.05$ for all comparisons).

In the correlation sub-study of pNfL with neuroimaging and neuropsychological evaluations, 25 PHIV+ and 23 HIV-negative controls were evaluated. Sociodemographic characteristics are described in Table 2. In relation to NT, we found that PHIV had significantly lower FI, but both groups had average results. Differences between groups in Stroop test performance were observed, but not in Coding. The mean PS composite z-score was lower in the PHIV group (Mean Z-score - 0.68 (SD 0.98)) compared to the HIV-negative group (Mean Z-score 0.00 (SD 1.00)) ($p < 0.05$)

Table 2
Means (standard deviations) of demographic, psychosocial, neurocognitive and psychopathological characteristics.

	PHIV (n = 25)	HIV- (n = 23)	P value
Sex (female) (% , n)	64 (16)	56,5 (13)	0.597
Age at assessment	21.0 (3.03)	20.9 (2.66)	0.522
Level of education (% , n)	N = 24	N = 21	0.146
Low	62.5 (15)	76.2 (16)	
Medium	16.7 (4)	0 (0)	
High	20.8 (5)	23.8 (5)	
Annual Income (% , n)	N = 23	N = 22	0.135
Low	43.5 (10)	59.1 (13)	
Medium	30.4 (7)	36.4 (8)	
High	26.1 (6)	4.5 (1)	
Caucasian (% , n)	72 (18)	56,5 (13)	0.263
Fluid Intelligence *	-0.72 (1.13)	0.01 (0.98)	0.021
Stroop	-0.84 (1.09)	0.00 (0.99)	0.009
Coding	-0.31 (0.86)	-0.12 (1.14)	0.512
Composite Processing Speed Z-score	-0.68 (0.98)	-0.00 (1.00)	0.025

Regarding brain volumes, the HIV infected group had significantly lower regional white matter volumes in left and right cerebellum ($p = 0.030$, $p = 0.028$), lateral occipital lobe ($p = 0.020$), left and right nucleus accumbens ($p = 0.010$, $p < 0.001$),

left and right occipital lobe ($p = 0.020$, $p = 0.042$) and left postcentral gyrus ($p = 0.022$), but no significant differences were found in total white matter volumes.

In the HIV group, Spearman's correlation test revealed negative association between pNfL concentrations and different regional white matter volumes of left and right cerebellum ($r = -.440$, $p = 0.028$; $r = -.0386$, $p = 0.056$), left and right brainstem ($r = -.440$, $p = 0.028$; $r = -.417$, $p = 0.038$) and right nucleus accumbens ($r = -.403$, $p = 0.046$) Fig. (2), and also a negative correlation was found between pNfL concentration and Coding score ($r = -.425$, $p = 0.039$). This association between NfL and brain volumes and coding score persisted when controlling for undetectable viral load.

Discussion

NfL is a neurofilament subunit particularly abundant in axons²⁰. Plasma NfL concentration was recently reported as a potential prognostic biomarker of disease onset and progression in neurodegenerative diseases including HIV^{4–8}.

In this study, we have shown that treated and virologically suppressed PHIV people, presented pNfL concentrations similar of those found in HIV-negative individuals. In addition, even considering the limitation of the small sample, patients with detectable viral load had higher pNfL levels, showing that persistent viral replication may contribute to neuronal damage.

This has been demonstrated similarly in the HIV adult population, in which the HIV-driven axonal degeneration can be halted by cART, which correlates to reduced CSF and pNfL concentrations over time after cART initiation^{5,21–22}. These results emphasize the importance of an early and continuous antiretroviral therapy to avoid neuronal damage in children.

In this exploratory study of PHIV adolescents and young adults, we found that higher pNfL concentration was significantly associated with lower regional brain volume and lower coding score. Similarly, Anderson *et al.* published that a higher pNfL was significantly associated with worse neuropsychological performance in the HIV adult population²³.

High concentration of NfL has been shown in multiple neurological diseases where processing speed is also one of the most affected cognitive processes, such as amyotrophic lateral sclerosis (ALS)^{24,25} (Menke *et al.*, 2015; Lu *et al.*, 2015), Alzheimer's disease²⁶ (Mattsson *et al.*, 2017) and frontotemporal dementia²⁷ (Rohrer *et al.*, 2016). Processing speed performance is considered to depend to a large extent on the properties of the white matter^{28–30} (Posthuma *et al.*, 2003; Borghesani *et al.*, 2013; Jacobs *et al.*, 2013). White matter includes myelinated axons in the brain, and the thickness of the myelin sheath is associated with nerve conduction velocity; therefore, its relation to processing speed and NfL seems consistent. Hence plasma NfL could be a feasible biomarker of milder neurocognitive alterations in the PHIV population.

Likewise, increased NfL levels and reduced brain volume in cortical and subcortical grey matter and within the white matter has been found in patients with different neurodegenerative conditions^{31–32}.

However, research performed in the HIV adult population found that CSF neuronal damage biomarkers, including NfL, were not associated with imaging measures of brain structures³³.

It should be noted that NfL has the limitation that it is not a disease-specific biomarker. As we have mentioned, elevated NfL is observed in many other neurological disorders, including neurodegenerative diseases, peripheral neuropathy, and traumatic brain injuries^{6,34}.

Regarding brain volumes we found that the HIV group showed WM atrophy in selected brain regions despite being on cART for years. Some studies performed in adolescents living with PHIV has reported similar results showing lower white matter volumes when compared with HIV negative controls^{35,36}.

Limitations of this study include the small sample size and lack of longitudinal biomarker data. The small sample size has been partially compensated for by strict selection criteria for the control group. Moreover, other limitations of the study are that this age group is potentially more likely to be involved in sports with head trauma, and this group of population may have different stressors, that have not been measured. Number of adverse childhood events (ACEs) would be a useful marker but has not been used. These are potentially important considerations in the adolescent age group during a time of dynamic myelination.

Finally, this current work was exploratory and therefore multiple statistical tests were performed, which might have resulted in type I errors.

Strengths of our study are, the inclusion of young adults living with PHIV, who have not previously been examined regarding plasma NfL levels, and that we were able to correlate brain volumes and processing speed in this population.

This research is representative of most young adults living with HIV vertically infected in developed healthcare systems. Moreover, thanks to the current great improvements in the diagnosis and treatment of HIV infection, this population that were born in the preTAR era making the study unique.

Conclusions

We can conclude that the ultrasensitive method to measure pNfL concentration provides an easily accessible biomarker in perinatally HIV infected patients avoiding lumbar puncture. Nevertheless, it remains unclear how pNfL varies in the PHIV population with virologic suppression or how its levels could be influenced in this population by the earlier initiation of effective antiretroviral therapy. Therefore, larger longitudinal studies are required in this group to further evaluate pNfL as a clinically useful biomarker of neurological deterioration.

Declarations

Ethics approval and consent to participate:

The Institutional Review Boards (IRBs) of each research centre approved the study and written informed consent was obtained from all participants. Where participants were underage, an assent form was signed by themselves, with legal guardians providing the informed consent in accordance with the Helsinki Declaration.

Consent for publication:

We hereby verify that the manuscript has not been submitted or accepted elsewhere. All authors have given consent for its publication.

Availability of data and material:

The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Competing interests:

a) NeuroCoRISpe group declare no competing financial interest.

b) The Sahlgrenska Academy at the University of Gothenburg group have no

competing interests that could be construed as influencing the contents of this paper. However, the authors list the following general potential conflicts of interest:

HZ has served on scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

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Authors' contributions:

BRS, MMB, MGT, MM conceptualized and designed the study, participated in analysis and interpretation of the data, drafted the initial manuscript and contributed and approved the final manuscript as submitted. BRS, MMB, MG, HZ, KB, AMA, SOJ, SAL, MAM, HM, JTR, MLN, MIGT were involved in the provision of study subjects, reviewed the manuscript drafts, and approved the final manuscript as submitted. All authors read and approved the final manuscript

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Figures

Figure 1

Plasma NfL concentrations in 3 different groups: HIV-negative control group, PHIV patients with detectable VL, and PHIV patients with undetectable viral load

*lCbe: left cerebellum; rCbe: right cerebellum; lBst: left brainstem; rBst: right Brainstem

Figure 2

Spearman correlations for cerebellum and brainstem volumetric measures and pNfL concentrations in HIV-infected patients

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