

HIV-1 infection-antiretroviral therapy's effect on the blood-brain barrier's integrity

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Telissa S. HIV-1 infection- antiretroviral therapy's effect on the blood-brain barrier's integrity. *Neurosurg J.* 2022; 5(2):11-13.

ABSTRACT

Injuries to the Blood-Brain Barrier (BBB) are common in HIV-Associated Dementia (HAD) patients and are a common characteristic of HIV encephalitis. BBB degradation can also be seen in HIV-infected people who are asymptomatic and not on Antiretroviral medication (ART). The goal of this study was to look

at the BBB's integrity before and after starting ART in both neuroasymptomatic HIV infection and HAD patients. In longitudinally monitored neuroasymptomatic HIV-1-infected persons and patients with HAD, BBB integrity was assessed by comparing cerebrospinal fluid (CSF)/plasma albumin ratios in archived CSF samples prior to and after beginning of ART. We also looked at HIV RNA in the blood and CSF, the IgG Index, CSF WBC counts, and 2-micoglobulin, neopterin, and neurofilament light chain protein quantities in the CSF (NfL).

INTRODUCTION

During primary infection, the Human Immunodeficiency Virus type 1 (HIV-1) invades the Central Nervous System (CNS). In type 1 - (HIV-1) invades the Central Nervous System (CNS). In the absence of therapy, this develops into a chronic infection and inflammation that can compromise the Blood-brain Barrier's integrity (BBB). The BBB's degeneration is most likely complex, with contributory factors including infected cells' release of pro-inflammatory cytokines and viral proteins, as well as HIV's direct infiltration of neurovascular unit cells, particularly pericytes and perivascular macrophages. Increased levels of neopterin in the Cerebrospinal Fluid (CSF) indicate intrathecal immune activation, which is linked to BBB damage [1]. The influx of proteins, viral particles, and other potentially neurotoxic substances from the blood into the CNS is facilitated by a non-intact BBB, increasing the risk of cellular injury, including axon disruption, which can be sensitively assessed using Neuro-filament Light chain protein measurement (NfL) [2]. BBB integrity, intrathecal immune activation, and CSF NfL concentrations have all been linked in studies, implying a link between CNS inflammation, BBB deterioration, and neuronal injury. Prior to the introduction of current Antiretroviral medication (ART), 30 to 40 percent of AIDS patients developed dementia caused by the virus (HAD). In individuals with HIV encephalitis, BBB integrity is compromised, and the BBB has been demonstrated to play a key role in the pathophysiology and development of HAD, albeit the process is yet unknown.

Although we previously observed that 68 percent of people with Exhibited had evidence of BBB impairment, we discovered no link between immune suppression and an elevated albumin ratio in untreated neuro-asymptomatic people, of whom 16 percent had signs of BBB impairment. ART decreases HIV RNA levels in the CSF as well as biomarkers of intrathecal inflammation and neuronal damage in the CSF. Despite effective antiretroviral therapy and undetectable virus levels in blood and CSF, many people continue to exhibit immunological activation, both systemically and in the CNS. The BBB has been discovered to be changed in up to one-third of untreated neuroasymptomatic people in previous investigations. Only a few case reports have looked at the effect of ART on the BBB, with patients with HAD showing normalised BBB function after starting ART [3]. The goals of our research were to a) assess the effect of ART on BBB integrity over time, b) investigate how changes in BBB integrity are linked to CNS inflammation and signs of neuronal injury in both neuroasymptomatic HIV-infected people and people with HAD, and c) see if starting ART can improve or even normalise BBB function.

METHODS

Nephelometry was used to make quantitative measurements of CSF and plasma albumin (Behring Nephelometer Analyser, Behringwerke

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Received: 04-April-2022, Manuscript No. PULNJ-22-4340; Editor assigned: 06-April-2022, PreQC No. PULNJ-22-4340(PQ); Reviewed: 13-April-2022, QC No. PULNJ-22-4340(Q); Revised: 15-April-2022, Manuscript No. PULNJ-22-4340(R); Published: 29-April-2022, DOI: 10.37532/pulnj.22.5(2).11-13



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AG, Marburg, Germany). To assess BBB function, the albumin ratio was determined as CSF albumin (mg/L)/plasma albumin (g/L). Individuals under the age of 45 had a reference value of 6.8 while those over 45 had a reference value of 10.2. According to the manufacturer's instructions, CSF neopterin was measured using a commercially available immunoassay. 5.8 nmol/L is the usual upper reference value for CSF neopterin. With age adjusted values, the concentration of CSF NfL was determined using a sandwich enzyme-linked immunosorbent assay (NF-light ELISA kit, UmanDiagnostics AB, Ume, Sweden). The top normal reference value was 823 ng/L, and the mean adjusted age was 44 years. The Roche Amplicor Monitor version 1.5 (Roche Molecular Systems, Branenburg, NJ), Abbott RealTime HIV-1 test (Abbott Laboratories, Abbott Park, IL), or Roche Taqman assay, version 1 or 2 were used to measure HIV RNA levels in blood and CSF (Hoffman La-Roche, Basel, Switzerland). The lower limit of quantification has evolved over time as new PCR methods have been implemented, ranging from 20 to 200 HIV RNA copies/mL depending on the test. A plasma HIV RNA level below the limit of detection, determined with the technology in use at the time, was described as viral suppression. The N Latex 2M kit on the Atellica NEPH 630 System was used to quantify CSF 2-microglobulin (Siemens Healthcare GmbH, Erlangen, Germany). At the local clinical laboratory, CD4+ T-cell counts, CSF leukocytes (WBC), IgG index, and CSF/blood albumin assays were performed. The IgG index was developed as [CSF IgG (mg/L)/serum IgG (g/L)] as a metric of intrathecal IgG production [albumin (mg/L) in CSF/albumin (g/L) in serum]. IgG Index had a reference value of 0.63 regardless of age, while CSF 2-microglobulin had a reference value of 1.2 mg/L for people 18-49 years old and 1.8 mg/L for people 50 years old.

Statistical analysis

Prism, version 9.0 (GraphPad, La Jolla, CA), SPSS, version 27 (IBM, Armonk, NY), and R, version 4.0, were used to perform descriptive statistics. To decrease skewness, all continuous variables except age and leukocyte count were log10 transformed. Pearson correlation coefficients were used to examine the relationships. Wilcoxon signed rank test was used to evaluate over time at 6 months and 3 years with interpolated values using LOCF (last observation carried forward) if all values were prior to these time points. Independent Student's t-test was used to compare two groups, and Wilcoxon signed rank test was used to evaluate over time at 6 months and 3 years with interpolated values using LOCF (last observation carried forward) if all values were prior to these time points [4,5].

RESULTS

Only cross-sectional data were available for 67 of the persons with HAD who had lumbar punctures either pre-ART (n=47) or during ART (n=20). For neuroasymptomatic persons, the median (interquartile range [IQR]) follow-up was 25 months (8-59), with a maximum follow-up of 15 years for those taking ART. The median follow-up for people with HAD was 8 (2-33) months, with a maximum follow-up on ART of 11 years. When compared to neuroasymptomatic participants, untreated individuals with HAD had significantly higher CSF HIV RNA (p<0.0001), albumin ratio (p<0.0001), CSF neopterin (p<0.0001), and CSF NfL (p<0.0001), as well as significantly lower CD4+ T-cell count (p<0.0001) and CD4 nadir (p<0.0001), and significantly lower CD4+ T-cell count (p<0.0001).

Neuroasymptomatic individuals

At baseline, 12 percent (10/82) of the longitudinally monitored neuroasymptomatic individuals had an increased albumin ratio. These

10 had similar baseline characteristics as the others in the neuroasymptomatic sample. At the time of the last follow-up, 9% (7/82) of the participants had abnormal albumin ratios. The albumin ratio fell considerably after starting ART, as evaluated at two time points: 6 months (p 0.05) and 3 years (p 0.01). CSF HIV RNA (p 0.001, p 0.001), CSF neopterin (p 0.001, p 0.001), CSF 2-microglobulin (p 0.001, p 0.001), WBC (p 0.001, p 0.001), and CSF NfL (p 0.01, p 0.001) all dropped considerably at the same time periods. At 6 months, there was a trend toward a substantial decrease in the IgG index (p=0.06) [6]. There was a substantial association between albumin ratio and age (r=0.4, p=0.001) and an inverse link between albumin ratio and IgG Index (r=-0.4, p=0.001). There were no relationships between albumin ratio and CSF NfL, inflammatory markers such as CSF neopterin, 2-microglobulin, or WBC, plasma or CSF HIV RNA, CD4+ T-cell count, or CD4 nadir, or plasma or CSF HIV RNA, CD4+ T-cell count, or CD4 nadir. At baseline, eight of the 10 people with HAD who were followed longitudinally had an increased albumin ratio. Untreated people with HAD who had only one cross-sectional lumbar puncture had increased albumin ratios in 68 percent (32/47) of cases. 25% (5/20) of patients with only one lumbar puncture who were taking ART showed increased albumin ratios in the cross-sectional HAD cohort. At the last follow-up, 20% (2/10) of the longitudinal Showed cohort had increased albumin ratios. The albumin ratio decreased after 6 months, but not considerably, and significantly after 3 years (p 0.05) in these ten persons with HAD who were followed longitudinally [7].

DISCUSSION

Only a small percentage of neuroasymptomatic people (12%) had high albumin ratios before starting ART, compared to 80 percent of people with HAD. This is similar to a recent cross-sectional study (n=631) in which 16 percent of untreated neuroasymptomatic people had higher albumin ratios. It's also in line with other research. However, 39 percent of 44 ART-naive individuals in an Italian research exhibited increased albumin ratios. One explanation for the discrepancy could be that lumbar punctures were performed in our two studies for research purposes, whereas they were performed in the Italian study for clinical purposes, such as the investigation of neurocognitive disorders; for differential diagnosis, such as epilepsy, hepatic, or vascular encephalopathy. In addition, one-third of the individuals admitted to abusing intravenous drugs [8]. The latter has the potential to compromise the BBB's integrity. Only four people in our sample, all of whom had HAD, had a history of drug misuse, and one reported ongoing drug use. Another recent Italian study found that 35% of 147 ART-naive people had BBB damage. Only 6% of the patients, however, were neuroasymptomatic. The other individuals had a range of CNS diseases, such as neurosyphilis, opportunistic infections, and HIV-associated Neurocognitive Disorders (HAND), making comparisons to our investigations challenging. The immunological state and other baseline data of the neuroasymptomatic people whose BBB was damaged at baseline were identical. There was a slight, but not significant, difference in age between those with elevated albumin ratios and those with normal albumin ratios, with a median age of 40 years for those with elevated albumin ratios compared to 38 years for those with normal albumin ratios, which would not explain the discrepancy in baseline levels of albumin ratios [9]. The duration of HIV infection could not be determined, which could explain the disparity. Another possibility is that the BBB degradation has nothing to do with HIV infection. We previously discovered that albumin ratios in neuro-asymptomatic HIV-infected people are similar to those in HIV-negative people. Individuals with HAD had a lower albumin ratio, but it wasn't statistically significant until the second time point, at 3 years, showing that BBB recovery takes longer in people with HAD. In people with HAD, viral replication occurs largely in brain tissue cells or tissue macrophages, rather than in the CSF, as it does in neuroasymptomatic people.

This could explain why HIV RNA decrease is slower after starting ART. Despite this, the majority (75%) of patients who had increased albumin ratios at baseline had them normalised after starting ART. Maintaining homeostasis in the CNS and protecting the brain from potentially harmful chemicals requires an intact BBB. It is made up of a semipermeable layer that surrounds the CNS and is made up of a highly specialised capillary bed. The endothelial cells are connected by tight junctions. When HIV infects cells in the peripheral and central nervous systems, viral proteins such as Tat, Gp120, and Nef are generated. They can harm the BBB by influencing less tight junctions and enabling permeability when combined with inflammatory mediators (e.g., cytokines and chemokines). This allows more blood and viral proteins, as well as other potentially harmful compounds, to enter the CNS [10].

CONCLUSION

In conclusion, albumin ratios decreased considerably following commencement of ART in both neuro-asymptomatic HIV-infected persons and patients with HAD, albeit the latter group's reduction took longer, indicating that healing may be delayed in those with a more severe BBB impairment. This would reaffirm the importance of the BBB in neuroinflammation and neuronal damage.

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