ASYMPTOMATIC CSF HIV-1 ESCAPE: INCIDENCE AND EFFECTS ON CNS BIOMARKERS

574

For additional information, please contact:
gustaf.ulfhammer@gu.se

Gustaf Ulfhammer[1,2], Arvid Edén[1,2], Aylin Yilmaz[1,2], Åsa Mellgren[1,2], Erika Tyrberg[1,2], Erik Sörstedt[1,2], Lars Hagberg[1,2], Johanna Gostner[3], Dietmar Fuchs[3], Henrik Zetterberg[4,5], Staffan Nilsson[6], Kristina Nyström[1], Magnus Gisslén[1,2,7]

[1]Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [2]Region Västra Götaland, Sahlgrenska University Hospital, Department of Infectious Diseases, Gothenburg, Sweden.
[3]Institute of Biological Chemistry, Biocenter, Innsbruck Medical University, Innsbruck, Austria. [4]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden. [5]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden.
[6]Department of Laboratory medicine, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [7]Public Health Agency of Sweden, Solna, Sweden.

Background

Elevated levels of HIV RNA can occasionally be detected in cerebrospinal fluid (CSF) despite viral suppression in plasma by antiretroviral therapy (ART), a condition termed 'CSF HIV-1 escape´ (CSF-E). In rare cases CSF-E is associated with clinical neurological disease (symptomatic CSF-E) but more commonly, no neurological symptoms are evident (asymptomatic CSF-E) [1-3].

Previous studies on asymptomatic CSF-E have been limited in size, leaving its incidence and clinical relevance unclear [4].

Purpose

Our objectives were to determine the incidence of CSF-E in a large, well-characterized Swedish cohort of people living with HIV (PLWH), and to evaluate its impact on CSF biomarkers indicative of central nervous system (CNS) inflammation and injury.

Method

A retrospective, longitudinal cohort analysis of neuroasymptomatic PLWH who had been successfully treated with ART for >6 months (plasma HIV RNA <50 copies/mL prior to inclusion) and who underwent CSF examinations for research purposes between 2016–2022 [5]. CSF-E was defined as either increased CSF HIV RNA with concurrent plasma suppression or as CSF HIV RNA exceeding that in plasma when both were detectable [6]. The lower limit of quantification for HIV RNA was 20 copies/mL. Linear mixed-effects models and generalized estimating equations were used to analyze repeated measurements of CSF neopterin, CSF neurofilament light protein (NfL), albumin ratio and CSF white blood cell (WBC) count.

CONCLUSIONS

IN THIS COHORT, **ASYMPTOMATIC CSF HIV-1 ESCAPE (CSF-E) WAS RARE** AND USUALLY RESOLVED WITHOUT TREATMENT ADJUSTMENTS. ASSOCIATIONS WERE OBSERVED BETWEEN CSF-E AND BIOMARKERS INDICATIVE OF CNS INFLAMMATION AND BLOOD-BRAIN BARRIER DAMAGE, BUT, IMPORTANTLY, NOT WITH BIOMARKER SIGNALING NEURONAL INJURY.

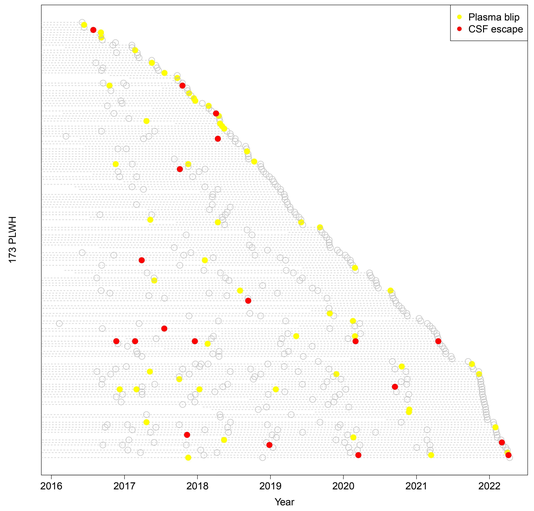


Figure 1. Overview of samples representing cerebrospinal fluid escape and viral plasma blips in the study population. The y-axis depicts the 173 people living with HIV (abbreviated PLWH in the figure) on stacked dashed horizontal lines, contingent upon their entry into the study, while the x-axis represents the study period. Each circle represents an individual sample. Empty grey circles indicate HIV-RNA < 20 copies/mL in both plasma and cerebrospinal fluid, red filled circles indicate CSF escape, and yellow filled circles indicate plasma blips. The total number of samples was 449. Fourteen (8.1%) had ≥ 1 samples with CSF-E and in total 19 samples out of 449 (4.2%) represented CSF-E.

Results

In total, 449 samples from 173 PLWH (65% male) were included (Figure 1). Mean number of samples per study participant was 2.6 (range 1–7) where ≥2 samples were collected from 114 PLWH.

CSF-E was present in 14 out of 173 PLWH (8.1%) with a median (IQR) CSF HIV RNA of 30 (25–55) copies/mL. Out of 449 samples, CSF-E was present in 19 (4%, Figure 2). One individual had ≥2 consecutive samples with CSF-E but remained clinically stable and did not require any treatment adjustment.

Samples with CSF-E exhibited a 25% higher geometric mean for CSF neopterin compared to those without CSF-E (P = 0.01), and an 8% higher geometric mean albumin ratio (P = 0.04).There were no significant differences in CSF NfL levels with respect to the presence or absence of CSF-E (P = 0.8). The odds ratio for detectable CSF WBC (≥3 × 10^6 cells/L) with CSF-E was 3.9 (P = 0.004).

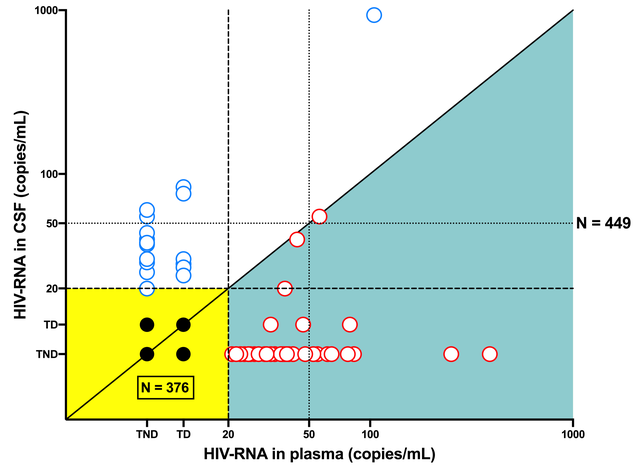


Figure 2. Relationship between cerebrospinal fluid (CSF) HIV-RNA (y-axis) and plasma HIV-RNA (x-axis) among the 449 samples. The densely dashed line indicates the lower limit of quantification (LLQ) of 20 copies/mL and the dotted line indicates the widely utilized cut-off of 50 copies/mL. The labels 'TD' and 'TND' on both axes represent 'target detected but not quantifiable' and 'target not detected' respectively. The four black filled circles (yellow background) represent 376 samples where HIV-RNA levels were below LLQ in both CSF and plasma. The empty blue circles (white background) represent samples with CSF-E (n=19) and empty red circles (turquoise background) represent samples with plasma HIV-RNA > LLQ and greater than CSF HIV-RNA (n=54).

SAHLGRENSKA ACADEMY
INSTITUTE OF BIOMEDICINE

REGION VÄSTRA GÖTALAND
SAHLGRENSKA UNIVERSITY HOSPITAL

References

1. Edén A, Fuchs D, Hagberg L, et al. *HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment.* J Infect Dis, 2010; 202:1819-25.
2. Perez-Valero, I., et al., *Cerebrospinal fluid viral escape in aviremic HIV-infected patients receiving antiretroviral therapy: prevalence, risk factors and neurocognitive effects.* AIDS, 2019. 33(3): p. 475-481.
3. Edén, A., et al., *Asymptomatic Cerebrospinal Fluid HIV-1 Viral Blips and Viral Escape During Antiretroviral Therapy: A Longitudinal Study.* J Infect Dis, 2016. 214(12): p. 1822-1825.
4. Trunfio, M., et al., *Cerebrospinal fluid HIV-1 escape according to different thresholds and underlying comorbidities: is it time to assess the definitions?* Aids, 2019. 33(4): p. 759-762.
5. Hagberg, L. and M. Gisslen, *Cohort profile: a longitudinal study of HIV infection in the central nervous system with focus on cerebrospinal fluid - the Gothenburg HIV CSF Study* BMJ Open 2023; 13:e070693.
6. European AIDS Clinical Society. *EACS Guidelines - Version 12.0 - October 2023.* EACS 2023. Available at https://www.eacsociety.org/media/guidelines-12.0.pdf.

UNIVERSITAS GOTHOBURGENSIS 1891
UNIVERSITY OF GOTHENBURG