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CONCISE COMMUNICATION

Cerebrospinal fluid proteomics reveals inflammatory activation in aneurysmal subarachnoid hemorrhage irrespective of HIV status

Rohen Harrichandparsad[a], Gil Lustig[b], Victoria Sviridchik[c], Zesuliwe Jule[d], Mallory Bernstein[d], Kajal Reedoy[d], Yashica Ganga[d], Afrah Khairallah[d], Farina Karim[d], Vinod B. Patel[e], Ahmed Iqbal Bhigjee[e], Duncan Royston[f], Khadija Khan[d] and Alex Sigal[c,d]

Objectives: People with HIV (PWH) are at increased risk of cerebrovascular abnormalities, including aneurysmal subarachnoid hemorrhage (SAH). However, it is unclear whether HIV-associated inflammation contributes significantly to the inflammatory response observed in the cerebrospinal fluid (CSF) during aneurysm rupture. Here, we used high-throughput Olink proteomics to compare inflammatory marker profiles in CSF between participants with aneurysmal SAH and PWH without aneurysms.

Design: This was a cross-sectional observational study which enrolled participants who were indicated for endovascular coil embolization due to ruptured anterior communicating artery aneurysms ($n = 30$) or who underwent clinically indicated lumbar puncture as part of the workup for nonneurovascular conditions ($n = 9$).

Methods: We performed a lumbar puncture and analyzed CSF samples from individuals presenting with aneurysmal SAH ($n = 30$) and PWH without any known vascular disorder ($n = 9$). Among the aneurysm patients, 13 were PWH and 17 were HIV-negative. An Olink Target 96 Inflammation panel was used to quantify inflammatory proteins.

Results: Among 68 detectable inflammatory proteins, 43 were significantly upregulated in participants with aneurysms ($n = 30$) compared to PWH without aneurysm ($n = 9$). A similar inflammatory signature was observed in HIV-negative aneurysm participants ($n = 17$) and PWH with aneurysm ($n = 13$), with no significant differences between these two groups. Interleukin-6 (IL-6) was the most upregulated protein across all aneurysm to nonaneurysm comparisons. These findings suggest that aneurysm rupture is associated with a strong CSF inflammatory response, largely independent of HIV status.

[a]Department of Neurosurgery, University of KwaZulu-Natal, Durban, South Africa, [b]Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, [c]The Lautenberg Center for Immunology and Cancer Research, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, [d]Africa Health Research Institute and University of KwaZulu-Natal, [e]Department of Neurology, University of KwaZulu-Natal, and [f]Department of Radiology, Lake Smit & Partners, Durban, KwaZulu-Natal, South Africa.

Correspondence to Rohen Harrichandparsad, MbChB, MMed, University of KwaZulu-Natal Nelson R Mandela School of Medicine: University of KwaZulu-Natal College of Health Sciences, Durban, KwaZulu-Natal, South Africa.

E-mail: Harrichandparsad@ukzn.ac.za

Received: 3 October 2025; revised: 17 December 2025; accepted: 27 December 2025.

DOI:10.1097/QAD.0000000000004445

Conclusion: Ruptured intracranial aneurysms are associated with strong upregulation of inflammatory proteins in the CSF. This inflammatory response appears independent of HIV infection.

AIDS 2026, **40**:787–791

Keywords: cerebrospinal fluid proteomics, endovascular coil embolization, HIV and aneurysmal subarachnoid hemorrhage, HIV-associated neuroinflammation, O-link inflammation panel

Introduction

Cerebrovascular complications, such as aneurysmal subarachnoid hemorrhage (SAH), pose significant health risks, particularly for people with HIV (PWH), who are known to have an increased incidence of cerebrovascular abnormalities [1–4].

Aneurysms are thought to occur due to disruptions in wall shear stress (WSS) of blood vessels in the central nervous system (CNS), explaining their high tendency to occur at vessel branch points [5–7]. Other mechanisms of aneurysm formation include genetic predisposition, segmental vulnerability, extracellular matrix failure, and remodeling failure [8–13]. Disruptions in WSS lead to endothelial dysfunction and a proinflammatory response mediated by NFB [5,6,14]. These events have been shown to increase the levels of proinflammatory mediators, including interleukin-6 (IL-6), a canonical activator of the NFB pathway [15,16]

The extent to which HIV-associated inflammation influences the inflammatory response in the CSF during intracranial aneurysm rupture remains poorly understood. Previous studies have suggested that HIV infection may exacerbate systemic and CNS inflammation, potentially amplifying the inflammatory cascade triggered by SAH [17–21].

To understand the effects of HIV status during intracranial aneurysm rupture, we enrolled a cohort of participants indicated for endovascular coil embolization due to ruptured anterior communicating artery aneurysms from Durban South Africa, an area with high HIV prevalence [22]. We used Olink proteomics to characterize and compare inflammatory marker profiles in the CSF of individuals with ruptured anterior communicating artery aneurysms, with and without HIV infection, and PWH without neurovascular pathology. Our results confirmed a strong pro-inflammatory response following SAH, but no apparent modulation of this response by HIV infection.

Materials and methods

Informed consent and ethical statement

This was an observational study with longitudinal sample collection. The study protocol for blood and CSF and matched blood collection from participants indicated for SAH surgery was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (reference BE480/15). Adult patients (>18 years old) presented at Inkosi Albert Luthuli Central Hospital in Durban, South Africa, Departments of Neurosurgery and Neurology. Written informed consent was obtained from all enrolled participants. The potential increased risk of aneurysm rupture associated with CSF drainage was discussed with all participants. This risk was minimized by avoiding sudden reductions in the transmural pressure gradient during CSF release. An 18-gauge spinal needle was used, and CSF drainage was performed in a controlled manner. No participant experienced aneurysm rupture attributable to CSF drainage. Patient discomfort was eliminated by performing all CSF-related study procedures under general anesthesia, concurrently with the endovascular intervention. CSF and matched blood were obtained from participants indicated for nonaneurysm-associated lumbar puncture enrolled at Inkosi Albert Luthuli Central Hospital and King Edward VIII Hospital in Durban, South Africa after obtaining written informed consent (University of KwaZulu-Natal Institutional Review Board approval BE385/13).

Participants

We analyzed CSF samples (1–5 ml) and matched blood samples from individuals presenting with aneurysmal SAH ($n = 30$) and PWH without any known vascular pathology ($n = 9$). Among the aneurysm participants, 13 were PWH and 17 were HIV-negative.

HIV viral load

Viral load was quantified at an accredited diagnostic laboratory (Molecular Diagnostic Services, Durban, South Africa), using the real-time HIV-1 viral load test on an Abbott machine.

Olink proteomics

An Olink Target Inflammation panel was used to quantify 92 inflammatory proteins. Proteomic data obtained from the Olink platform were processed using the limma package in R. False discovery rate (FDR) correction was performed using the Benjamini–Hochberg method. Proteins detected in less than 75% of the samples were excluded, yielding 68 analyzable markers. For these proteins, any individual measurements below the limit of

detection (LOD) were set to the LOD value. The results were graphed using ggplot in R.

Results

We enrolled 30 participants with SAH, of which 13 were PWH and 17 were HIV-negative. Written informed consent was obtained from all enrolled participants. Enrollment was performed prior to the indicated surgical procedure of endovascular coil embolization, and a CSF sample was taken at enrollment. Median time between rupture and CSF draw was 5 [interquartile range (IQR) 3–8] days. In addition, nine PWH were enrolled for clinical indications for lumbar puncture and were characterized in a previous study [23]. These participants were admitted to the Neurology department for work-up of nonneurovascular conditions like thoracic myelopathy. Clinically indicated lumbar puncture was performed as part of the work-up. The median age was 42 years in the aneurysm group and 41 years in the no aneurysm group, with no significant difference between them. Likewise, the proportion of men was approximately 40% and was not different for any of the groups. The median HIV viral load was undetectable (threshold of detection = 40 HIV RNA copies/ml) in PWH with and without aneurysms. However, there was a borderline significant difference in this parameter because there were five HIV-viremic individuals in the aneurysm group.

We quantified 92 inflammatory proteins in the CSF from individuals with SAH and people with HIV (PWH) without vascular disease using the Olink Target Inflammation panel. After exclusion of proteins detected in less than 75% of the samples, 68 markers were analyzed. Compared with PWH without aneurysms, 43 proteins were significantly upregulated in the combined aneurysm group (Fig. 1a). A similar pattern was observed in subgroup analyses: 34 proteins were elevated in aneurysm PWH relative to PWH without aneurysms (Fig. 1b) and 43 in HIV-negative participants with aneurysm (Fig. 1c) relative to PWH without aneurysm. A direct comparison between PWH with aneurysm and HIV-negative aneurysm patients revealed no differentially expressed proteins (Fig. 1d).

The top five most upregulated proteins in each aneurysm comparison showed marked fold-changes and largely overlapped between the subgroups (Fig. S1, http://links.lww.com/QAD/D777). NPX (Normalized Protein eXpression, the unit used by Olink proteomics assays to report protein abundance) distributions for all significant proteins demonstrated consistent elevation across aneurysm patients. In all aneurysm-related comparisons, IL-6 showed the highest fold-change, followed by chemokines and cytokines including CXCL6, MCP-3, LIF, and CXCL1 (Fig. 1 and Fig. S1, http://links.lww.com/QAD/D777). These findings indicate that aneurysmal SAH triggers a robust and consistent inflammatory response in the CSF, which is not substantially modified by concurrent HIV infection.

We also examined the effect of HIV viremia on protein expression. The group of viremic PWH with SAH showed no significantly regulated proteins after FDR correction relative to the combined group of suppressed PWH with SAH and HIV-negative participants with SAH, HIV-negative participants with SAH, and suppressed PWH with SAH (Fig. S2, http://links.lww.com/QAD/D777). However, there was upregulation in inflammatory marker proteins including IL-6 when the viremic PWH with SAH were compared to suppressed PWH without SAH (Figs. S2 and S3, http://links.lww.com/QAD/D777).

Discussion

This study revealed a robust inflammatory signature in the CSF of individuals with aneurysmal SAH, characterized by the upregulation of classical proinflammatory cytokines, most notably IL-6. Despite the known immune activation associated with HIV, PWH with aneurysms exhibited a near-identical CSF inflammatory profile to that of HIV-negative aneurysm patients. This suggests that the local response to aneurysm rupture overrides any HIV-specific effects within the CNS compartment. This may indicate that the inflammation we measure is a postneurovascular event phenomenon whose scale masks any differences in inflammation between PWH and HIV-negative individuals pre-SAH.

The limitations of the study include a small sample size and no HIV-negative nonaneurysm group. Furthermore, there were several viremic participants in the PWH aneurysm group whereas all PWH without aneurysm were HIV-suppressed in the plasma. However, given that the differences persisted between the HIV-negative aneurysm group and the PWH nonaneurysm group, it is unlikely that this HIV viremia in the PWH aneurysm group was responsible for the pronounced difference in inflammatory markers. Furthermore, there were no differentially expressed proteins between viremic PWH with aneurysm compared to either suppressed PWH with aneurysm or HIV-negative participants with aneurysm. The levels of inflammatory proteins increased when viremic PWH with aneurysm were compared to PWH without aneurysm, showing that significant differences in expression could still be detected despite the low number of participants per group.

Finally, we are measuring inflammation postrupture and investigating the effect of HIV status on this inflammation.

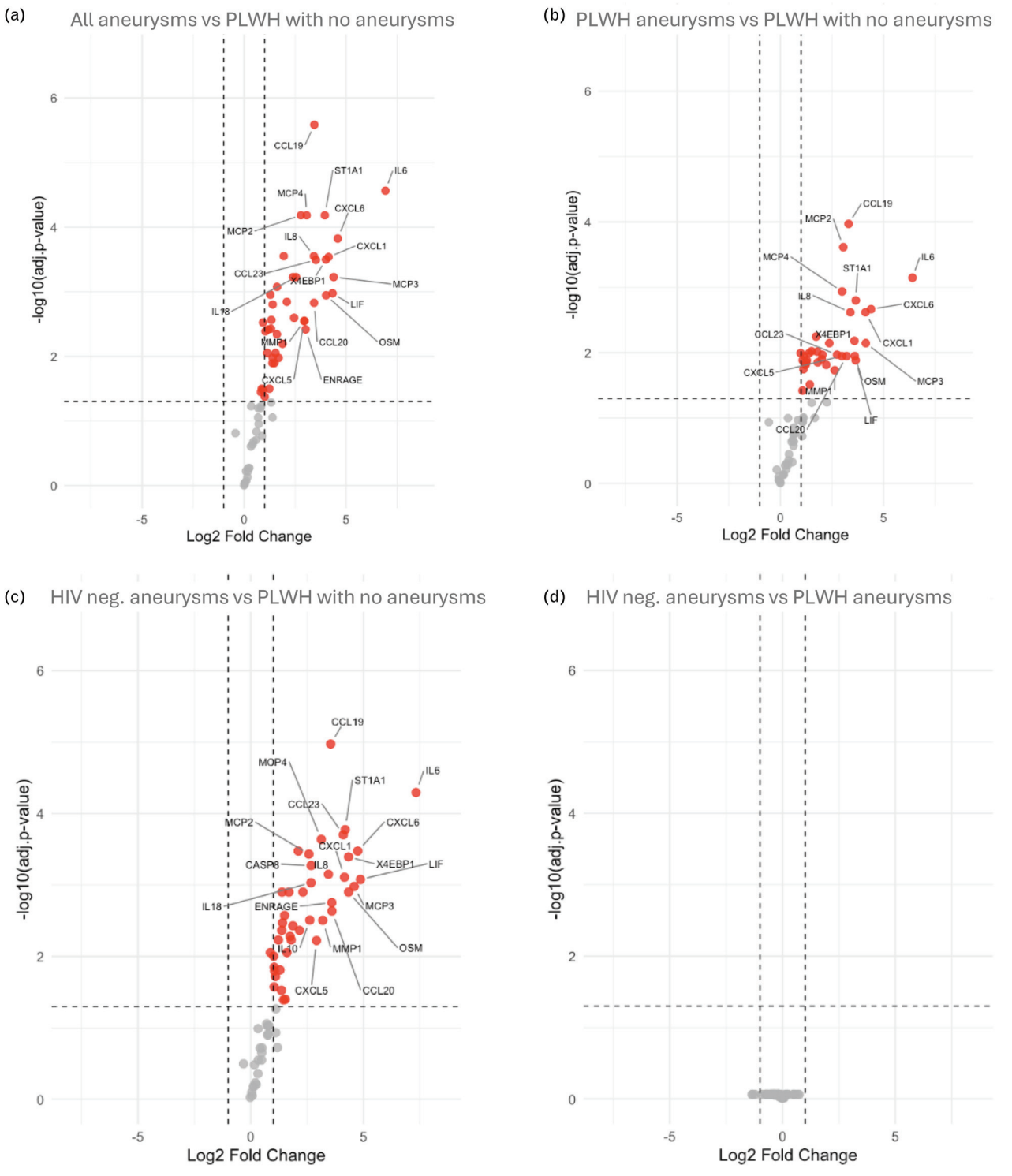

Fig. 1. Volcano plots showing differentially expressed inflammatory proteins between groups. (a) All aneurysm participants versus PWH without aneurysm. (b) PWH with aneurysm participants versus PWH without aneurysm. (c) HIV-negative aneurysm participants versus PWH without aneurysm. (d) HIV-negative participants with aneurysm versus PWH with aneurysm. *x*-axis is logged fold change and *y*-axis is logged FDR-adjusted *P* value. FDR, false discovery rate; PWH, people with HIV.

We cannot deduce from the data whether HIV had an effect on the inflammatory profile prerupture.

Our findings demonstrate that aneurysmal subarachnoid hemorrhage elicits a robust pro-inflammatory response within the CNS, characterized by the widespread upregulation of inflammatory mediators in the cerebrospinal fluid (CSF). IL-6 emerged as the most prominently elevated cytokine across all aneurysm-related comparisons, consistent with its established role as a key driver of neuroinflammation, glial activation, and secondary brain injury following CNS insults [24,25].

Our findings underscore the importance of inflammation in the pathogenesis and clinical course of aneurysmal SAH and suggest that HIV status does not substantially alter this response.

Acknowledgements

We would like to acknowledge the CNS and SAH study participants and study staff.

Author contributions: R.H.: conceptualization/study design, data interpretation, wrote first draft. G.L.: conceptualization/study design, data interpretation. V. S.: analyzed experimental data generated. Z.J.: performed experiments. M.B.: setup and managed the cohort and cohort data. K.R: performed experiments. Y.G.: performed experiments. A.K.: analyzed experimental data generated. F.K.: setup and managed the cohort and cohort data. V.B.P.: study infrastructure, data collection, critical review, and edits. A.I.B.: conceptualization/study design, critical review, and edits. D.D.R.: conceptualization/study design, critical review, and edits. K.K.: conceptualization/study design, data interpretation. A. S.: conceptualization/study design, data interpretation, critical review, and edits.

Funding: this work was supported by the National Institutes of Health award 5R01AI138546 (AS).

Conflicts of interest

There are no conflicts of interest.

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