



HAL
open science

Editorial: Biomarkers for prognosis of neuroinflammation and neurodegeneration associated with acute and chronic viral diseases

Otávio de Melo Espíndola, Juliana Echevarria-Lima, Philippe V Afonso

► To cite this version:

Otávio de Melo Espíndola, Juliana Echevarria-Lima, Philippe V Afonso. Editorial: Biomarkers for prognosis of neuroinflammation and neurodegeneration associated with acute and chronic viral diseases. *Frontiers in Neuroscience*, 2024, 18, 10.3389/fnins.2024.1354409 . pasteur-04712342

HAL Id: pasteur-04712342

<https://pasteur.hal.science/pasteur-04712342v1>

Submitted on 27 Sep 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



OPEN ACCESS

EDITED BY

Guo-Yuan Yang,
Shanghai Jiao Tong University, China

REVIEWED BY

Qian Luo,
Qingdao University, China
Wei Zhu,
Huazhong University of Science and
Technology, China

*CORRESPONDENCE

Otávio de Melo Espindola
✉ otavio.espindola@ini.fiocruz.br
Philippe V. Afonso
✉ philippe.afonso@pasteur.fr

RECEIVED 12 December 2023

ACCEPTED 08 January 2024

PUBLISHED 16 January 2024

CITATION

Espindola OM, Echevarria-Lima J and Afonso PV (2024) Editorial: Biomarkers for prognosis of neuroinflammation and neurodegeneration associated with acute and chronic viral diseases.
Front. Neurosci. 18:1354409.
doi: 10.3389/fnins.2024.1354409

COPYRIGHT

© 2024 Espindola, Echevarria-Lima and Afonso. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Editorial: Biomarkers for prognosis of neuroinflammation and neurodegeneration associated with acute and chronic viral diseases

Otávio de Melo Espindola^{1*}, Juliana Echevarria-Lima² and Philippe V. Afonso^{3*}

¹Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil, ²Department of Immunology, Instituto de Microbiologia Paulo de Góes, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, ³Unité Epidémiologie et Physiopathologie des Virus Oncogènes, Institut Pasteur, Université Paris-Cité, CNRS UMR 3569, Paris, France

KEYWORDS

biomarkers, central nervous system, neuroinflammation, neurodegeneration, virus infection, prognostic markers, blood-brain-barrier

Editorial on the Research Topic

[Biomarkers for prognosis of neuroinflammation and neurodegeneration associated with acute and chronic viral diseases](#)

Many RNA and DNA viruses exhibit neuroinvasive properties and can be associated with acute or chronic neurological manifestations (Debiasi and Tyler, 2004). Therefore, rapid identification of pathogens causing central nervous system (CNS) disorders is crucial, and prognostic biomarkers are helpful for early disease management and follow-up of therapeutic interventions. However, studying biomarkers of neurodegenerative and neuroinflammatory processes related to viral infections is challenging due to the limited number of experimental models, difficulty in accessing the human CNS, and brain tissues being available generally postmortem (Rauf et al., 2022).

When studying neurodegenerative diseases triggered by viral infections, many factors should be considered. A factor that may potentialize CNS infection is the viral inoculum, which is too often disregarded. For instance, mouse models only develop neurological symptoms when infected with high doses of virus Yellow Fever virus (YFV), suggesting that a certain plasma YFV concentration is necessary for neuroinvasion (Douam et al., 2017). The route of infection on the one hand is also crucial. Neural cells may be directly exposed such as the olfactory cells, as described for human beta-coronaviruses (Desforger et al., 2014). Moreover, neurons may be infected through neuron-to-neuron transfer, as shown for herpes simplex and rabies viruses (Ugolini, 2011). Finally, neurons may be infected by blood-borne virus after bypassing the blood-brain-barrier (BBB), for example through infection of BBB endothelial cells, or transmigration of infected leukocytes in a “Trojan horse” strategy, as observed for Nipah virus (Mathieu et al., 2011), HTLV-1 (Afonso et al., 2008), and flaviviruses (Maximova and Pletnev, 2018). Some viruses can be highly neurotropic to immature CNS, such as the Zika virus (Garcez et al., 2016; Schuler-Faccini et al., 2016). Moreover, the site of infection may also be key in the development of symptoms. In this sense, Sha and Chen, at the Chongqing Three Gorges University,

China, reviewed aspects of infection by all seven coronaviruses with the ability to infect humans, including routes of infection, neuroinvasion mechanisms, structural properties of viral proteins associated with virulence, and potential drug inhibition pathways.

Biomarkers for neurological involvement in viral infections often overlap with those of classical neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, multiple sclerosis, and amyotrophic lateral sclerosis. These include cerebrospinal fluid (CSF) and serum levels of Tau protein, neurofilament light and heavy chain proteins, intrathecal IgG production, astrocytic activation markers, and factors associated with microglial activation (Gomes et al., 2022; Gaur et al., 2023; O'Day, 2023). However, there are differences when considering acute infection and long-term progression, and the mechanisms may be distinct. While it seems easier to recapitulate acute diseases, one has to be more careful when considering long-progressing diseases. In particular, the many correlations between markers and diseases may not evidence a direct role of these elements. For instance, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) richly illustrates a virus-induced long-term progressive neurodegenerative disease. HAM/TSP presents with motor disability and sensory, urinary, intestinal, and sexual disturbances. This clinical picture results from the continuous neuronal damage and gliosis of the thoracic and lumbar tracts of the spinal cord due to the response of cytotoxic CD8⁺ T-cells (CTLs) against infected CD4⁺ T-cells at sites of inflammation (Souza et al., 2021). Therefore, biomarkers for HAM/TSP development or progression rely mostly on inflammation markers (Tamaki et al., 2019; Souza et al., 2021; Freitas et al., 2022; Gomes et al., 2022). Silva De Castro et al. in a collaboration between the Federal University of Rio de Janeiro, Brazil, and the National Cancer Institute, Bethesda, MD, United States, investigated the effect of HTLV-1 infection on the cellular prion protein (PrP^C) expression by CD4⁺ T-cells. It was observed that PrP^C levels were lower in HTLV-1-infected cells as well as the frequency of PrP^C+ CD4⁺ T-cells, and it was induced in an IFN type II dependent manner by the HTLV-1 Orf I encoded p12 protein, which is associated with HTLV-1 persistence by favoring cell proliferation and the immune escape by promoting MHC class I degradation. Therefore, these results open a new direction in the investigation of the potential role of PrP^C-associated pathways in the neuropathogenesis of HTLV-1 infection.

Biomarkers might also have distinct predictive values considering the site of sample collection. Proteomic profiles and biomarker concentrations differ between the ventricular and lumbar CSF compartments (Rostgaard et al., 2023). Therefore, one should pay attention to the CNS-affected area. Sensing or responding to immune signals such as interferons (IFN) may also be divergent when considering the cortex, the spinal cord, or other regions, posing the problem of viral replication and antiviral responses. Telikani et al. at La Trobe University and the University of Sydney, Australia, reviewed CNS antiviral mechanisms, discussing different immune signatures according to the responsiveness of cell types or subtypes, tissue location, and differentiation stage. This review presents the main response mechanisms of CNS resident cells against RNA and DNA viruses, highlighting the role of astrocytes as the main IFN- β producers

in the brain, innate immune responses performed by microglial cells, the importance of autophagy by neuronal cell populations in the control of viral replication, and the role of glial cells in also promoting neuronal survival.

And finally, there is always a sweet spot between efficient intrathecal immune response and excessive inflammation. Despite the benefits of viral clearance, removal of cellular debris, and tissue repair, the consequences of neuroinflammation are primarily responsible for morbidity and mortality (Wyss-Coray and Mucke, 2002). Rocamonde et al. at the Université Lyon, France, reviewed the role of cytokine mediators in the development of inflammatory diseases in the CNS, the interactions between viruses and glial cells, and the mechanisms involved in exacerbated glial responses.

Overall, collaborative efforts of distinct research groups have helped to identify prognostic biomarkers and the mechanisms behind neurological involvement associated with distinct viral infections, yet many remain unclear. This Research Topic covers a range of original articles and reviews that discuss the current knowledge over the impact of viral infections on the CNS, highlighting the influence of routes of infection, target cells, mechanisms of immune response promoted by CNS resident cells, and the modulation of cellular functions. We believe that information organized in this Research Topic might contribute to support future investigations of biomarkers for CNS degeneration and inflammation associated with viral infections.

Author contributions

OE: Writing—original draft. JE-L: Writing—review & editing. PA: Writing—original draft, Writing—review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Programa Jovem Cientista do Nosso Estado—FAPERJ—Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (Grant: E-26/200.157/2023).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Afonso, P. V., Ozden, S., Cumont, M.-C., Seilhean, D., Cartier, L., Rezaie, P., et al. (2008). Alteration of blood-brain barrier integrity by retroviral infection. *PLoS Pathog.* 4, e1000205. doi: 10.1371/journal.ppat.1000205
- Debiasi, R. L., and Tyler, K. L. (2004). Molecular methods for diagnosis of viral encephalitis. *Clin. Microbiol. Rev.* 17, 903–925. doi: 10.1128/CMR.17.4.903-925.2004
- Desforges, M., Le Coupanec, A., Stodola, J. K., Meessen-Pinard, M., and Talbot, P. J. (2014). Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res.* 194, 145–158. doi: 10.1016/j.virusres.2014.09.011
- Douam, F., Soto Albrecht, Y. E., Hrebikova, G., Sadimin, E., Davidson, C., Kotenko, S. V., et al. (2017). Type III interferon-mediated signaling is critical for controlling live attenuated yellow fever virus infection *in vivo*. *MBio* 8, e00819-17. doi: 10.1128/mBio.00819-17
- Freitas, N. L., Gomes, Y. C. P., Souza, F. D. S., Torres, R. C., Echevarria-Lima, J., Leite, A. C. B., et al. (2022). Lessons from the cerebrospinal fluid analysis of HTLV-1-infected individuals: biomarkers of inflammation for HAM/TSP development. *Viruses* 14, 2146. doi: 10.3390/v14102146
- Garcez, P. P., Loiola, E. C., Madeiro da Costa, R., Higa, L. M., Trindade, P., Delvecchio, R., et al. (2016). Zika virus impairs growth in human neurospheres and brain organoids. *Science* 352, 816–818. doi: 10.1126/science.aaf6116
- Gaur, A., Rivet, L., Mah, E., Bawa, K. K., Gallagher, D., Herrmann, N., et al. (2023). Novel fluid biomarkers for mild cognitive impairment: a systematic review and meta-analysis. *Ageing Res. Rev.* 91, 102046. doi: 10.1016/j.arr.2023.102046
- Gomes, Y. C. P., Freitas, N. L., Souza, F. S., Sandim, V., Pereira, D. A., Nogueira, F. C. S., et al. (2022). Chitotriosidase 1 in the cerebrospinal fluid as a putative biomarker for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) progression. *Front. Immunol.* 13, 949516. doi: 10.3389/fimmu.2022.949516
- Mathieu, C., Pohl, C., Szecsi, J., Trajkovic-Bodennec, S., Devergnas, S., Raoul, H., et al. (2011). Nipah virus uses leukocytes for efficient dissemination within a host. *J. Virol.* 85, 7863–7871. doi: 10.1128/JVI.00549-11
- Maximova, O. A., and Pletnev, A. G. (2018). Flaviviruses and the central nervous system: revisiting neuropathological concepts. *Annu. Rev. Virol.* 5, 255–272. doi: 10.1146/annurev-virology-092917-043439
- O'Day, D. H. (2023). Protein biomarkers shared by multiple neurodegenerative diseases are calmodulin-binding proteins offering novel and potentially universal therapeutic targets. *J. Clin. Med.* 12, 7045. doi: 10.3390/jcm12227045
- Rauf, A., Badoni, H., Abu-Izneid, T., Olatunde, A., Rahman, M. M., Painuli, S., et al. (2022). Neuroinflammatory markers: key indicators in the pathology of neurodegenerative diseases. *Molecules* 27, 3194. doi: 10.3390/molecules27103194
- Rostgaard, N., Olsen, M. H., Ottenheijm, M., Drici, L., Simonsen, A. H., Plomgaard, P., et al. (2023). Differential proteomic profile of lumbar and ventricular cerebrospinal fluid. *Fluids Barr. CNS* 20, 6. doi: 10.1186/s12987-022-00405-0
- Schuler-Faccini, L., Ribeiro, E. M., Feitosa, I. M. L., Horovitz, D. D. G., Cavalcanti, D. P., Pessoa, A., et al. (2016). Possible association between Zika virus infection and microcephaly - Brazil, 2015. *MMWR Morb. Mortal. Wkly. Rep.* 65, 59–62. doi: 10.15585/mmwr.mm6503e2
- Souza, F. D. S., Freitas, N. L., Gomes, Y. C. P., Torres, R. C., Echevarria-Lima, J., Silva-Filho, I. L., et al. (2021). Following the clues: usefulness of biomarkers of neuroinflammation and neurodegeneration in the investigation of HTLV-1-associated myelopathy progression. *Front. Immunol.* 12, 737941. doi: 10.3389/fimmu.2021.737941
- Tamaki, K., Sato, T., Tsugawa, J., Fujioka, S., Yagishita, N., Araya, N., et al. (2019). Cerebrospinal fluid CXCL10 as a candidate surrogate marker for HTLV-1-associated myelopathy/tropical spastic paraparesis. *Front. Microbiol.* 10, 2110. doi: 10.3389/fmicb.2019.02110
- Ugolini, G. (2011). Rabies virus as a transneuronal tracer of neuronal connections. *Adv. Virus Res.* 79, 165–202. doi: 10.1016/B978-0-12-387040-7.00010-X
- Wyss-Coray, T., and Mucke, L. (2002). Inflammation in neurodegenerative disease—a double-edged sword. *Neuron* 35, 419–432. doi: 10.1016/S0896-6273(02)00794-8