



HAL
open science

Severe Malaria with Neurological Manifestations: What Contribution of Neurofilament Light Chain?

Souheil Zayet, Beate Hagenkötter, Isabelle Quadrio, Vincent Gendrin,
Timothée Klopfenstein

► To cite this version:

Souheil Zayet, Beate Hagenkötter, Isabelle Quadrio, Vincent Gendrin, Timothée Klopfenstein. Severe Malaria with Neurological Manifestations: What Contribution of Neurofilament Light Chain?. *Journal of Infectious Diseases*, 2024, 229 (1), pp.294-295. 10.1093/infdis/jiad489 . hal-04801598

HAL Id: hal-04801598

<https://hal.science/hal-04801598v1>

Submitted on 27 Jan 2025

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.

Severe Malaria with Neurological Manifestations: What Contribution of Neurofilament Light Chain?

TO THE EDITOR—We have read with great interest the study conducted by Balanza et al, for the ROSI Study Group, entitled “Neurofilament light chain as a biomarker of neuronal damage in children with malaria” [1]. The authors have concluded that neurofilament light chain (NfL) levels increased over time in 167 children from Mozambique, aged 1–12 years, with uncomplicated (UM) and severe malaria (SM). They also elegantly demonstrated that the adjusted increase in NfL over 84 hours was higher in SM cases with neurological manifestations compared to SM without neurological manifestations and UM ($P = .001$ and $P = .010$, respectively). We would like to raise a few concerns for further discussion.

As specified by Balanza et al [1], we have recently described the only previous report, in human pathology, of NfL quantification in malaria in a traveler presenting with postmalaria acute motor axonal neuropathy [2]. In fact, the idea to perform this assay resulted from the cerebrospinal fluid (CSF) analysis, which revealed cytoalbumin dissociation with suspicion for postmalaria demyelinating polyneuropathy. This was in collaboration with, and thanks to the expertise of, the Laboratory of Neurobiology and Neurogenetics, Department of Biochemistry and Molecular Biology, Lyon University Hospital, who had already demonstrated that elevation of CSF biomarkers of neuroinflammation and a rise of CSF NfL is indicative of neuronal damage in coronavirus disease 2019 (COVID-19) patients with neurological symptoms [3], and also in other pathologies including cognitive disorders (frontotemporal dementia) and/or motor impairments (amyotrophic lateral

sclerosis) [4]. NfL remains a neuron-specific protein, but its determination in the context of malaria seems to be interesting [5]. It is certainly not possible to extrapolate conclusions from a single case, but the strong point in the study of our patient remains the correlation analysis between the high levels of NfL and the abnormal findings on electrophysical examination, which led us to appropriate immunoglobulin treatment. It seems appropriate to associate NfL changes with electroencephalogram or electromyography results to better quantify damage in the central and/or peripheral nervous systems.

In our opinion, the conclusions reached by Balanza et al [1] should be considered with caution. First, clinical features differ in SM with neurological manifestations in children and adults. The authors do not provide sufficient details in their clinical description in their Table 1 (except number of seizures in the preceding 24 hours, impaired consciousness, and coma). The role of NfL as a neurochemical marker of cerebral and/or axonal injury should be considered in SM with neurological presentation, but cannot probably be generalized to all clinical forms of cerebral malaria such as delayed cerebellar ataxia or postmalaria neurological syndrome. However, among SM patients, the adjusted increase in NfL over time was clearly higher in patients with neurological signs ($P = .001$, $P < .001$, and $P < .001$ for repeated seizures, coma, and impaired consciousness, respectively) than in patients without neurological signs with demonstrated longitudinal regression lines.

The study of a population of children from Mozambique may also reveal another limitation in the analysis of plasma NfL levels; it is known that concentrations of CSF and serum NfL increase with age in healthy patients, with an

increase in adult control serum NfL levels of 2.2% per year of age [6–8].

In addition, the authors reported 2 deaths in the SM group with neurological manifestations (2.4%). It would be interesting to have more details on the NfL values and to assess whether NfL levels could be useful in determining the illness prognosis as a risk factor for mortality.

Finally, the occurrence of a past history of malaria in these patients could contribute to cumulative neuronal damage, which also remains to be proven, contrary to our patient who is Caucasian with no previous episode of malaria.

The limited evidence in the literature and the results presented by the authors suggest that measurement of NfL levels in plasma and/or CSF may be useful to identify and quantify brain injury in malaria. It would be interesting to determine a neurological prognosis with threshold/cutoff of NfL. Due to the decreased level during the first days of hospitalization and the difficulty of performing this measurement in practice, NfL measurements would not likely be added to the World Health Organization severity criteria in children [9, 10]. However, it could be a neurological prognostic biomarker in SM patients after a few days of hospitalization; for example, 5 days after admission according to longitudinal regression lines in Balanza et al [1] (that is, in their Figure 1B and 1C, among SM patients, increase in NfL over time was higher in patients with impaired consciousness or coma 120 hours after admission). Clinical data of children on follow-up, especially long-term neurological damage considered by Balanza et al and associated with NfL plasma levels, would be helpful to determine if NfL could be a neurological prognosis biomarker in SM.

Notes

Financial support. No financial support was received for this work.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Souheil Zayet,¹ Beate Hagenkötter² Isabelle Quadrio,³ Vincent Gendrin,¹ and Timothée Klopfenstein¹

¹Department of Infectious Diseases, Nord Franche-Comté Hospital, Trevenans, France; ²Department of Neurology, Nord Franche-Comté Hospital, Trevenans, France; and ³Laboratory of Neurobiology and Neurogenetics, Department of Biochemistry and Molecular Biology, Lyon University Hospital, Bron, France

References

1. Balanza N, Francis CK, Crowley VM, et al. Neurofilament light chain as a biomarker of neuronal damage in children with malaria. *J Infect Dis* **2024**; 229:183–8.
2. Zayet S, Klopfenstein T, Quadrio I, et al. Post malaria acute motor axonal neuropathy. *J Travel Med* **2022**; 29:taac056.
3. Chaumont H, Kaczorowski F, San-Galli A, et al. Cerebrospinal fluid biomarkers in SARS-CoV-2 patients with acute neurological syndromes. *Rev Neurol (Paris)* **2023**; 179:208–17.
4. Escal J, Fourier A, Formaglio M, et al. Comparative diagnosis interest of NfL and pNfH in CSF and plasma in a context of FTD-ALS spectrum. *J Neurol* **2022**; 269:1522–9.
5. Comeau D, Martin M, Robichaud GA, Chamard-Witkowski L. Neurological manifestations of post-acute sequelae of COVID-19: which liquid biomarker should we use? *Front Neurol* **2023**; 14:1233192.
6. Yilmaz A, Blennow K, Hagberg L, et al. Neurofilament light chain protein as a marker of neuronal injury: review of its use in HIV-1 infection and reference values for HIV-negative controls. *Expert Rev Mol Diagn* **2017**; 17:761–70.
7. Disanto G, Barro C, Benkert P, et al. Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis. *Ann Neurol* **2017**; 81:857–70.
8. Barro C, Benkert P, Disanto G, et al. Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. *Brain J Neurol* **2018**; 141:2382–91.
9. Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. *Trans R Soc Trop Med Hyg* **2000**; 94 (Suppl 1):S1–90.
10. World Health Organization. Guidelines for the treatment of malaria, **2015**. <https://apps.who.int/iris/handle/10665/162441m>. Accessed 13 September 2023.