



**HAL**  
open science

# A Letter Concerning a Role for Blood-Brain Barrier Dysfunction in Delirium following Noncardiac Surgery in Older Adults

Loic Le Guennec, Alexander Balcerac, Nicolas Weiss

► **To cite this version:**

Loic Le Guennec, Alexander Balcerac, Nicolas Weiss. A Letter Concerning a Role for Blood-Brain Barrier Dysfunction in Delirium following Noncardiac Surgery in Older Adults. *Annals of Neurology*, 2023, 3 (4), pp.303-312. 10.1002/ana.26837 . hal-04349730

**HAL Id: hal-04349730**

**<https://hal.sorbonne-universite.fr/hal-04349730v1>**

Submitted on 18 Dec 2023

**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.

## A Letter Concerning A Role for Blood-brain Barrier Dysfunction in Delirium following Non-Cardiac Surgery in Older Adults

#Loïc Le Guennec<sup>1,2,3</sup> Alexander Balcerac<sup>1,2,3</sup> and Nicolas Weiss<sup>1,2,3,4,5</sup>

<sup>1</sup>Sorbonne Université, AP-HP.Sorbonne Université, Faculté de Médecine, Hôpital de la Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital 75013 Paris, France.

<sup>2</sup>Médecine Intensive Réanimation à orientation Neurologique, Département de Neurologie, Hôpitalier de la Pitié-Salpêtrière, AP-HP.Sorbonne Université, Assistance Publique-Hôpitaux de Paris, 47-83 boulevard de l'Hôpital 75013 Paris, France.

<sup>3</sup>DMU Neurosciences, Institut de Neurosciences Translationnelles IHU-A-ICM, 47-83 boulevard de l'Hôpital 75013 Paris, France.

<sup>4</sup> Groupe de Recherche Clinique en Réanimation et Soins intensifs du Patient en Insuffisance Respiratoire aiguë (GRC-RESPIRE) Sorbonne Université.

<sup>5</sup> Brain Liver Pitié-Salpêtrière (BLIPS) Study Group, INSERM UMR\_S 938, Centre de recherche Saint-Antoine, Maladies métaboliques, biliaires et fibro-inflammatoire du foie, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France.

#Corresponding author : Loïc Le Guennec, MD, PhD, Médecine Intensive Réanimation Neurologique, Hôpital de la Pitié-Salpêtrière, 47, boulevard de l'Hôpital 75013 Paris, France

ORCID : 0000-0001-8146-6256 Phone: +33.1.84.82.79.18 e-mail: [loic.leguennec@aphp.fr](mailto:loic.leguennec@aphp.fr)

**Keywords:** Blood-Brain-Barrier; Albumin quotients

To the Editor,

Devinney et al. <sup>1</sup> highlight a link between blood-brain barrier (BBB) dysfunction and post-surgery delirium in older adults. Using the MADCO-PC and INTUIT studies, they analyzed cerebrospinal fluid (CSF) samples from before and after surgery. CSF-to-plasma albumin ratio (CPAR) was used as a surrogate for BBB dysfunction. In their study, 12.6% of subjects experienced postoperative delirium, with a significant rise in CPAR values post-surgery. This change correlated with delirium and longer hospital stays.

It should be specified that CPAR is an imperfect marker for BBB dysfunction for several reasons. First, CPAR evaluates the blood-CSF barrier (BCSFB) rather than the BBB <sup>2,3</sup>. It's essential to distinguish between the BBB and BCSFB, as they have different diffusion pathways and CSF flow rates. The authors suggest a continuous relationship between CPAR and BBB permeability, referencing a study by Montagne et al. <sup>4</sup> which shows a correlation between CPAR and a specific MRI sequence called "K<sub>trans</sub>". This sequence reflects the efflux rate of gadolinium from blood plasma into the brain's extravascular-extracellular space. Unfortunately, the generalization of these findings established on a population of normal aging subjects or subjects with various causes of cognitive impairment to patients undergoing surgery lacks evidence. Also, as discussed by Reiber and others <sup>5,6</sup>, CPAR doesn't consider CSF flow rate, and factors like reduced CSF production that can alter its values. Since CPAR focuses on albumin (70kDa), lower levels of increased permeability can be missed <sup>7,8</sup>. Olsson et al. <sup>9</sup> also showed that consecutive lumbar punctures within 24h-48h raised CPAR, possibly due to inflammation from the initial puncture.

Furthermore, Devinney's "2-hit" theory for delirium onset lacks data on peri-operative drugs. Indeed, some drugs, especially CYP3A or P-glycoprotein inhibitors <sup>10</sup>, are tied to delirium. Our team found that in conditions with increased BBB permeability, such drugs often appear in patient CSF <sup>11</sup>. Finally, the study omits details on the orthopedic surgeries performed, even though 27.1% of participants had them. Differentiating between spinal surgeries, which could be "neurosurgery" or "orthopedic surgery", is vital. Spinal surgeries might cause inflammation, affecting CSF-albumin levels.

In summary, Devinney's study provides really new insights in the pathophysiology of post-operative delirium. Nevertheless, it has gaps and potential biases. Given the complexities surrounding BBB and BCSFB, a singular approach may not capture the full extent of their dynamics and future studies should consider a multimodal

assessment approach: First, incorporate a broader range of blood biomarkers such as Protein S-100 Beta, Neuron specific enolase, and GFAP. These markers can provide a more comprehensive understanding of BBB and BCSFB integrity and function. Second, utilize advanced MRI sequences allowing to measure “ $K_{trans}$ ”. However, performing an MRI on a patient experiencing delirium is challenging, as their agitation can compromise the quality and safety of the imaging procedure. CT-Perfusion imaging<sup>12</sup> is feasible for agitated patients because it is fast, and allows BBB assessment. Third, account for the potential bias of drugs administered during the peri-operative period.

By integrating these additional measures, future research can offer a more holistic and accurate understanding of BBB and BCSFB dynamics in the context of postoperative delirium. It's essential to interpret the current data with caution, recognizing its limitations, and the potential for various biases. Only with a comprehensive approach can we truly unravel the complexities of BBB and BCSFB in relation to postoperative complications in older adults.

## References

1. Devinney MJ, Wong MK, Wright MC, et al. A Role for Blood-brain Barrier Dysfunction in Delirium following Non-Cardiac Surgery in Older Adults. *Annals of neurology*. 2023 Aug 24.
2. Weiss N, Miller F, Cazaubon S, Couraud PO. The blood-brain barrier in brain homeostasis and neurological diseases. *Biochimica et biophysica acta*. 2009 Apr;1788(4):842-57.
3. Le Guennec L, Weiss N. Blood–brain barrier dysfunction in intensive care unit. *Journal of Intensive Medicine*. 2023 2023/02/15/.
4. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015 Jan 21;85(2):296-302.
5. Reiber H. Proteins in cerebrospinal fluid and blood: barriers, CSF flow rate and source-related dynamics. *Restor Neurol Neurosci*. 2003;21(3-4):79-96.
6. Reiber H. Flow rate of cerebrospinal fluid (CSF)--a concept common to normal blood-CSF barrier function and to dysfunction in neurological diseases. *J Neurol Sci*. 1994 Apr;122(2):189-203.
7. Dadas A, Washington J, Diaz-Arrastia R, Janigro D. Biomarkers in traumatic brain injury (TBI): a review. *Neuropsychiatric disease and treatment*. 2018;14:2989-3000.
8. Shlosberg D, Benifla M, Kaufer D, Friedman A. Blood-brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nature reviews Neurology*. 2010 Jul;6(7):393-403.
9. Olsson M, Ärlig J, Hedner J, Blennow K, Zetterberg H. Repeated lumbar punctures within 3 days may affect CSF biomarker levels. *Fluids Barriers CNS*. 2019 Dec 13;16(1):37.
10. Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J. Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1, and ABCG2 genetic polymorphisms; and inflammatory factors. *Critical care medicine*. 2013 Apr;41(4):999-1008.
11. Weiss N, Barbier Saint Hilaire P, Colsch B, et al. Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy. *Journal of hepatology*. 2016 Dec;65(6):1120-30.
12. Wintermark M, Sincic R, Sridhar D, Chien JD. Cerebral perfusion CT: technique and clinical applications. *Journal of neuroradiology = Journal de neuroradiologie*. 2008 Dec;35(5):253-60.

## Disclosures:

Loïc Le Guennec has nothing to disclose.

Alexander Balcerac has nothing to disclose.

Nicolas Weiss declares having perceived consultant fees from MedDay Pharmaceuticals and Owkin.

LLG, AB and NW wrote the manuscript.