**Supplementary material**

**ACUTE ENCEPHALOPATHY IN THE ICU: A PRACTICAL APPROACH**

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Section: Acute Neurological Problems

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**PATHOPHYSIOLOGY OF ACUTE ENCEPHALOPATHY: COMMON MECHANISMS AND FINAL PATHWAYS**

The common final pathway explaining the acute change in global cognition in both coma and delirium involves altered neurotransmission with excitatory/inhibitory imbalance leading to ultimately leading to distintegration or dysfacilitation, that is the disruption of whole-brain dynamics within thalamo-cortico-striatal loops with subsequent reduced functional connectivity between key anatomical regions and neural networks subserving attention and consciousness (1-9). These are notably the basal forebrain, central thalamus and frontal parietal neocortical areas, the so-called meso-circuit (10-12), which is under the dependence of the dorsal brainstem arousal network (13-15). There is also accumulating evidence for an important role of the autonomic nervous system and its modulation by the limbic system (16).

Aside from direct diffuse or focal lesions to key anatomical structures and consciousness networks, several other precipitating factors can, in isolation or in combination, lead to the disruption of neural networks and neurotransmission. A precise description of all potential mechanisms falls beyond the scope of this review, but we will briefly mention some of them. Neuroinflammation is one of the proposed pathway implicated in AE (17). Systemic inflammation, whether due to an infection or to non-infectious conditions such as trauma or surgery, can lead to neuroinflammation through a humoral pathway (direct trafficking of peripheral cytokines to the brain neuroendocrine and autonomic centers through circumventricular organs and disrupted blood-brain barrier) and a neural pathway (inflammatory signaling and autonomic nervous system response through the vagus nerve)(18). Both results in brain structural and metabolic disturbances affecting neurons and astrocytes, with a pivotal role of microglial activation (19). These changes, located notably in the autonomic and cholinergic brainstem nuclei as well as in the limbic system (20-22), are thought to contribute both to the acute change in cognition and its associated features (dysautonomia, brainstem dysfunction (23) and to to the long-term consequences of AE (24, 25). Yet the relationship between the two is complex as markers of inflammation are indeed independently associated with AE in critically ill patients (24-28) but not to long-term cognitive decline (29) potentially because of dissociable effects of systemic inflammation on the brain (30). Impaired brain metabolism can also be a direct consequence of dysnatremia or cerebral bioenergetic insufficiency, either in case of hypoxemia or abnormal glucose metabolism (hypoglycemia or reduced glucose uptake notably in case of insulin insensitivity)(31, 32), ultimately leading to oxidative stress and mitochondrial dysfunction. Another proposed pathway is vascular changes, either in the macrocirculation (ischemia, decreased cerebral blood flow (33, 34), or impaired neurovascular coupling and autoregulation (35-37) or in the microcirculation with reduced tissue perfusion and endothelial dysfunction (38-40). AE can also result from the accumulation of neurotoxic chemicals (either drugs or metabolites), notably in case of increased production and/or reduced clearance. This is the case in Cefepime-induced encephalopathy which promotes excitotoxicity through the inhibition of GABA-A receptors and GABA-A release (41) or in hepatic encephalopathy in which ammonia accumulation overwhelms the astrocytes detoxification capacity leading to cytotoxic edema (42). Increased inhibitory tone can also be due to direct effect of GABAergic sedatives (43), such as benzodiazepines, which are a known risk factor of delirium (44) and which can cause long-term alteration of synaptic architecture (45). Several drugs can also impair excitatory neurotransmitter signaling, such as antihistaminic or anticholinergic drugs, and lead to delirium. In fact, cholinergic deficiency has been proposed as a major contributing factor of AE, closely related to inflammation and endothelium (46-49). Recently, increased activity of acetylcholinesterase have been found to be associated with the burden of AE in critically ill patients (50, 51) and pre-ICU exposure to donepezil was associated with a reduction of delirium during the ICU stay in patients with dementia in a retrospective cohort (52).

One of the hallmarks of AE is that all these mechanisms can be favored by an underlying predisposition, the most common being aging and dementia (53). Indeed, both are characterized by decreased baseline connectivity, vasculopathy and impaired astrocyte and microglial response to inflammation and neurotransmitter release.

All the aforementioned pathways are closely related and often combined such as in septic associated encephalopathy (54-56) or hepatic encephalopathy (57). Nevertheless, specific etiologies and clinical presentations may involve them differentially. The role of dopaminergic transmission may thus differ between coma and delirium, and among delirium motor subtypes, while different biomarkers relates to delirium and long-term cognitive outcome in inflamed and non-inflamed patients (58).

In the end, AE is likely due to the breakdown of complex homeostasis (59), reflecting the inability of a (vulnerable) brain to show resilience in response to an acute stressor.

**REFERENCES**

1. Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A, et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology. 2010;113(5):1038-53.

2. Choi SH, Lee H, Chung TS, Park KM, Jung YC, Kim SI, et al. Neural network functional connectivity during and after an episode of delirium. Am J Psychiatry. 2012;169(5):498-507.

3. van Dellen E, van der Kooi AW, Numan T, Koek HL, Klijn FA, Buijsrogge MP, et al. Decreased functional connectivity and disturbed directionality of information flow in the electroencephalography of intensive care unit patients with delirium after cardiac surgery. Anesthesiology. 2014;121(2):328-35.

4. Numan T, Slooter AJC, van der Kooi AW, Hoekman AML, Suyker WJL, Stam CJ, et al. Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. Clin Neurophysiol. 2017;128(6):914-24.

5. Young JWS. The network model of delirium. Med Hypotheses. 2017;104:80-5.

6. van Montfort SJT, van Dellen E, van den Bosch AMR, Otte WM, Schutte MJL, Choi SH, et al. Resting-state fMRI reveals network disintegration during delirium. Neuroimage Clin. 2018;20:35-41.

7. Demertzi A, Tagliazucchi E, Dehaene S, Deco G, Barttfeld P, Raimondo F, et al. Human consciousness is supported by dynamic complex patterns of brain signal coordination. Sci Adv. 2019;5(2):eaat7603.

8. Pais-Roldan P, Edlow BL, Jiang Y, Stelzer J, Zou M, Yu X. Multimodal assessment of recovery from coma in a rat model of diffuse brainstem tegmentum injury. Neuroimage. 2019;189:615-30.

9. van Montfort SJT, van Dellen E, Stam CJ, Ahmad AH, Mentink LJ, Kraan CW, et al. Brain network disintegration as a final common pathway for delirium: a systematic review and qualitative meta-analysis. Neuroimage Clin. 2019;23:101809.

10. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci. 2010;33(1):1-9.

11. Redinbaugh MJ, Phillips JM, Kambi NA, Mohanta S, Andryk S, Dooley GL, et al. Thalamus Modulates Consciousness via Layer-Specific Control of Cortex. Neuron. 2020;106(1):66-75 e12.

12. Fridman EA, Beattie BJ, Broft A, Laureys S, Schiff ND. Regional cerebral metabolic patterns demonstrate the role of anterior forebrain mesocircuit dysfunction in the severely injured brain. Proc Natl Acad Sci U S A. 2014;111(17):6473-8.

13. Snider SB, Bodien YG, Frau-Pascual A, Bianciardi M, Foulkes AS, Edlow BL. Ascending arousal network connectivity during recovery from traumatic coma. Neuroimage Clin. 2020;28:102503.

14. Snider SB, Bodien YG, Bianciardi M, Brown EN, Wu O, Edlow BL. Disruption of the ascending arousal network in acute traumatic disorders of consciousness. Neurology. 2019;93(13):e1281-e7.

15. Fischer DB, Boes AD, Demertzi A, Evrard HC, Laureys S, Edlow BL, et al. A human brain network derived from coma-causing brainstem lesions. Neurology. 2016;87(23):2427-34.

16. Candia-Rivera D. Brain-heart interactions in the neurobiology of consciousness. Curr Res Neurobiol. 2022;3:100050.

17. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. Acta Neuropathol. 2010;119(6):737-54.

18. Becher B, Spath S, Goverman J. Cytokine networks in neuroinflammation. Nat Rev Immunol. 2017;17(1):49-59.

19. Wolf SA, Boddeke HW, Kettenmann H. Microglia in Physiology and Disease. Annu Rev Physiol. 2017;79:619-43.

20. Carrara M, Ferrario M, Bollen Pinto B, Herpain A. The autonomic nervous system in septic shock and its role as a future therapeutic target: a narrative review. Ann Intensive Care. 2021;11(1):80.

21. Sharshar T, Annane D, de la Grandmaison GL, Brouland JP, Hopkinson NS, Francoise G. The neuropathology of septic shock. Brain Pathol. 2004;14(1):21-33.

22. Sharshar T, Gray F, Lorin de la Grandmaison G, Hopkinson NS, Ross E, Dorandeu A, et al. Apoptosis of neurons in cardiovascular autonomic centres triggered by inducible nitric oxide synthase after death from septic shock. Lancet. 2003;362(9398):1799-805.

23. Benghanem S, Mazeraud A, Azabou E, Chhor V, Shinotsuka CR, Claassen J, et al. Brainstem dysfunction in critically ill patients. Crit Care. 2020;24(1):5.

24. Bourhy L, Mazeraud A, Costa LHA, Levy J, Rei D, Hecquet E, et al. Silencing of amygdala circuits during sepsis prevents the development of anxiety-related behaviours. Brain. 2022;145(4):1391-409.

25. Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. J Neurosci. 2005;25(40):9275-84.

26. Girard TD, Ware LB, Bernard GR, Pandharipande PP, Thompson JL, Shintani AK, et al. Associations of markers of inflammation and coagulation with delirium during critical illness. Intensive Care Med. 2012;38(12):1965-73.

27. Khan BA, Perkins AJ, Prasad NK, Shekhar A, Campbell NL, Gao S, et al. Biomarkers of Delirium Duration and Delirium Severity in the ICU. Crit Care Med. 2020;48(3):353-61.

28. McGrane S, Girard TD, Thompson JL, Shintani AK, Woodworth A, Ely EW, et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care. 2011;15(2):R78.

29. Brummel NE, Hughes CG, Thompson JL, Jackson JC, Pandharipande P, McNeil JB, et al. Inflammation and Coagulation during Critical Illness and Long-Term Cognitive Impairment and Disability. Am J Respir Crit Care Med. 2021;203(6):699-706.

30. Skelly DT, Griffin EW, Murray CL, Harney S, O'Boyle C, Hennessy E, et al. Acute transient cognitive dysfunction and acute brain injury induced by systemic inflammation occur by dissociable IL-1-dependent mechanisms. Mol Psychiatry. 2019;24(10):1533-48.

31. Haggstrom LR, Nelson JA, Wegner EA, Caplan GA. 2-(18)F-fluoro-2-deoxyglucose positron emission tomography in delirium. J Cereb Blood Flow Metab. 2017;37(11):3556-67.

32. Sonneville R, de Montmollin E, Poujade J, Garrouste-Orgeas M, Souweine B, Darmon M, et al. Potentially modifiable factors contributing to sepsis-associated encephalopathy. Intensive Care Med. 2017;43(8):1075-84.

33. Takeuchi M, Suzuki H, Matsumoto Y, Kikuchi Y, Takanami K, Wagatsuma T, et al. Prediction of the development of delirium after transcatheter aortic valve implantation using preoperative brain perfusion SPECT. PLoS One. 2022;17(11):e0276447.

34. Yokota H, Ogawa S, Kurokawa A, Yamamoto Y. Regional cerebral blood flow in delirium patients. Psychiatry Clin Neurosci. 2003;57(3):337-9.

35. Ferlini L, Su F, Creteur J, Taccone FS, Gaspard N. Cerebral autoregulation and neurovascular coupling are progressively impaired during septic shock: an experimental study. Intensive Care Med Exp. 2020;8(1):44.

36. Pfister D, Siegemund M, Dell-Kuster S, Smielewski P, Ruegg S, Strebel SP, et al. Cerebral perfusion in sepsis-associated delirium. Crit Care. 2008;12(3):R63.

37. Schramm P, Klein KU, Falkenberg L, Berres M, Closhen D, Werhahn KJ, et al. Impaired cerebrovascular autoregulation in patients with severe sepsis and sepsis-associated delirium. Crit Care. 2012;16(5):R181.

38. Hughes CG, Morandi A, Girard TD, Riedel B, Thompson JL, Shintani AK, et al. Association between endothelial dysfunction and acute brain dysfunction during critical illness. Anesthesiology. 2013;118(3):631-9.

39. Hughes CG, Pandharipande PP, Thompson JL, Chandrasekhar R, Ware LB, Ely EW, et al. Endothelial Activation and Blood-Brain Barrier Injury as Risk Factors for Delirium in Critically Ill Patients. Crit Care Med. 2016;44(9):e809-17.

40. Hughes CG, Patel MB, Brummel NE, Thompson JL, McNeil JB, Pandharipande PP, et al. Relationships between markers of neurologic and endothelial injury during critical illness and long-term cognitive impairment and disability. Intensive Care Med. 2018;44(3):345-55.

41. Sugimoto M, Uchida I, Mashimo T, Yamazaki S, Hatano K, Ikeda F, et al. Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. Neuropharmacology. 2003;45(3):304-14.

42. Holecek M. Ammonia and amino acid profiles in liver cirrhosis: effects of variables leading to hepatic encephalopathy. Nutrition. 2015;31(1):14-20.

43. Craig MM, Misic B, Pappas I, Adapa RM, Menon DK, Stamatakis EA. Propofol sedation-induced alterations in brain connectivity reflect parvalbumin interneurone distribution in human cerebral cortex. Br J Anaesth. 2021;126(4):835-44.

44. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21-6.

45. Wenzel M, Leunig A, Han S, Peterka DS, Yuste R. Prolonged anesthesia alters brain synaptic architecture. Proc Natl Acad Sci U S A. 2021;118(7).

46. Cerejeira J, Nogueira V, Luis P, Vaz-Serra A, Mukaetova-Ladinska EB. The cholinergic system and inflammation: common pathways in delirium pathophysiology. J Am Geriatr Soc. 2012;60(4):669-75.

47. Chatterjee PK, Al-Abed Y, Sherry B, Metz CN. Cholinergic agonists regulate JAK2/STAT3 signaling to suppress endothelial cell activation. Am J Physiol Cell Physiol. 2009;297(5):C1294-306.

48. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, et al. Resolving postoperative neuroinflammation and cognitive decline. Ann Neurol. 2011;70(6):986-95.

49. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet. 2010;375(9716):773-5.

50. Muller A, Olbert M, Heymann A, Zahn PK, Plaschke K, von Dossow V, et al. Relevance of peripheral cholinesterase activity on postoperative delirium in adult surgical patients (CESARO): A prospective observational cohort study. Eur J Anaesthesiol. 2019;36(2):114-22.

51. Hughes CG, Boncyk CS, Fedeles B, Pandharipande PP, Chen W, Patel MB, et al. Association between cholinesterase activity and critical illness brain dysfunction. Crit Care. 2022;26(1):377.

52. Lieberman OJ, Lee S, Zabinski J. Donepezil treatment is associated with improved outcomes in critically ill dementia patients via a reduction in delirium. Alzheimers Dement. 2023;19(5):1742-51.

53. Singh TD, O'Horo JC, Gajic O, Sakusic A, Day CN, Mandrekar J, et al. Risk factors and outcomes of critically ill patients with acute brain failure: A novel end point. J Crit Care. 2018;43:42-7.

54. Barbosa-Silva MC, Lima MN, Battaglini D, Robba C, Pelosi P, Rocco PRM, et al. Infectious disease-associated encephalopathies. Crit Care. 2021;25(1):236.

55. Mazeraud A, Righy C, Bouchereau E, Benghanem S, Bozza FA, Sharshar T. Septic-Associated Encephalopathy: a Comprehensive Review. Neurotherapeutics. 2020;17(2):392-403.

56. Sonneville R, Benghanem S, Jeantin L, de Montmollin E, Doman M, Gaudemer A, et al. The spectrum of sepsis-associated encephalopathy: a clinical perspective. Crit Care. 2023;27(1):386.

57. Weiss N, Jalan R, Thabut D. Understanding hepatic encephalopathy. Intensive Care Med. 2018;44(2):231-4.

58. van den Boogaard M, Kox M, Quinn KL, van Achterberg T, van der Hoeven JG, Schoonhoven L, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. Crit Care. 2011;15(6):R297.

59. Eeles E, Teodorczuk A, Mitleton-Kelly E. Reconceptualizing delirium as a disorder of complex system failure. Med Hypotheses. 2018;118:121-6.