On the Road to a Delirium Assay

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Delirium, an acute disturbance in attention, awareness, and cognition that occurs as "a direct physiologic consequence of another medical condition, substance intoxication or withdrawal … or is due to multiple etiologies" (1), is a frequent complication of critical illness. Delirium's acute consequences, such as unplanned removal of endotracheal tubes and inability to intentionally engage in rehabilitative services, are likely the tip of a poorly understood iceberg. In numerous studies, delirium during critical illness has been strongly associated with long-term cognitive impairment in survivors as well as other components of post-intensive care syndrome (2–4). Yet, the pathophysiologic mechanisms underlying delirium remain unknown.

Multiple overlapping models have been put forward to explain delirium's pathogenesis (5); these implicate neuroinflammation and microglial activation, blood-brain barrier disruption, and depletion of neuroprotective mediators, among other mechanisms. Pathways that are activated in sepsis and acute respiratory distress syndrome, prototypal critical illness syndromes, are believed to be at work in delirium, and previous studies have found that elevations in markers of inflammation are associated with delirium. In addition to implicating inflammation, prior biomarker research examining S100B has supported the hypothesis that astrocyte injury and blood-brain barrier disruption play a role in delirium (6).

In this issue of *Critical Care Medicine*, Khan et al (7) report the results of a nested prospective cohort study during which they took a new approach when examining relationships between previously studied biomarkers and delirium. Within the subset of Pharmacological Management of Delirium trial (8) participants who had blood collected at study enrollment, the investigators analyzed associations between multiple biomarkers and both duration and severity of delirium. Specifically, they used the Confusion Assessment Measurement for the ICU (CAM-ICU) (9) to detect delirium and the CAM-ICU-7 (10) to grade delirium severity in 321 critically ill patients and measured interleukin (IL)–6,

IL-8, IL-10, tumor necrosis factor (TNF)–alpha, C-reactive protein, S100B, and insulin-like growth factor-1 in blood collected at enrollment.

After adjusting for age, gender, Acute Physiology and Chronic Health Evaluation II score, Charlson comorbidity score, sepsis, and study intervention group (which did not result in significant differences in the trial outcomes), they found that higher concentrations of IL-6, IL-8, IL-10, TNF-alpha, and S100B at study enrollment were associated with fewer delirium/coma-free days, a composite outcome used to avoid confounding by early death. The findings were similar when associations with average delirium severity were evaluated. Additionally, S100B predicted delirium/coma-free days and delirium severity even after 26 patients with overt neurologic damage were excluded. In summary, this investigation confirms previous reports that plasma concentrations of inflammatory biomarkers and S100B are associated with duration of delirium during critical illness and provides new evidence that these same biomarkers are associated with CAM-ICU-7 scores, a delirium severity tool previously associated with mortality.

With this study, Khan et al (7) advance the field in important ways. The connection between biomarkers measured early during critical illness and subsequent delirium severity is novel and suggests that an early blood-based assessment may have prognostic utility among ICU patients with delirium. Additionally, although biomarkers in cerebrospinal fluid might better reflect the brain's biochemical state, the study by Khan et al (7) adds to the growing body of evidence suggesting that plasma biomarkers can be used to measure brain injury (11, 12). A major question, however, was left unanswered by Khan et al (7): Do the plasma biomarkers that predict delirium duration and severity during critical illness also predict long-term cognitive impairment in survivors?

Up to one third of critical illness survivors struggle with persistent cognitive impairment (3). Given that delirium duration in the ICU predicts severity of cognitive impairment in survivors up to a year later (2, 3), biomarker research may identify mechanisms that are common to these short- and long-term manifestations of brain injury. Hughes et al (6, 13), for example, found that plasma S100B concentrations early during critical illness predicted not only delirium duration but also severity of long-term cognitive impairment. It remains unclear, however, whether the numerous inflammatory biomarkers associated with delirium are also predictors of—and thus, indicators of mechanisms leading to—long-term cognitive impairment.

Future studies of potential circulating biomarkers of brain injury during critical illness should assess long-term cognition, and samples should be collected at multiple timepoints. Khan et al, like previous investigators, identified that certain biomarkers measured at a single early timepoint are associated with subsequent cognitive outcomes, but a study that monitors changes in biomarker concentrations over time will likely yield additional important information about why delirium persists for some and resolves quickly for others. Although well-validated delirium assessment tools are widely used, their sensitivity varies in different settings (14, 15) and specificity of delirium as a predictor of long-term outcomes is limited. It is possible that a panel of plasma biomarkers can be used over time as a

laboratory assay for not only delirium but the acute brain injury that precedes long-term cognitive impairment.

As Khan et al (7) note, this study is unlikely on its own to change clinical practice. The results of the biomarker panel they studied would not be available at most centers until after a patient's delirium clears, and future studies are needed to examine the clinical utility of such a panel. Yet, with this work, the evidence implicating neuroinflammation and astrocyte injury as mechanisms of delirium during critical illness grows, and the field takes a step toward a delirium assay.

Acknowledgments

REFERENCES

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013

2. Girard TD, Jackson JC, Pandharipande PP, et al. : Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med 2010; 38:1513–1520 [PubMed: 20473145]

3. Pandharipande PP, Girard TD, Jackson JC, et al. ; BRAIN-ICU Study Investigators: Long-term cognitive impairment after critical illness. N Engl J Med 2013; 369:1306–1316 [PubMed: 24088092]

4. Brummel NE, Jackson JC, Pandharipande PP, et al. : Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. Crit Care Med 2014; 42:369–377 [PubMed: 24158172]

5. AGS/NIA Delirium Conference Writing Group, Planning Committee and Faculty: The American Geriatrics Society/National Institute on aging bedside-to-bench conference: Research agenda on delirium in older adults. J Am Geriatr Soc 2015; 63:843–852 [PubMed: 25834932]

6. Hughes CG, Pandharipande PP, Thompson JL, et al. : Endothelial activation and blood-brain barrier injury as risk factors for delirium in critically ill patients. Crit Care Med 2016; 44:e809–e817 [PubMed: 27088157]

7. Khan BA, Perkins AJ, Prasad NK, et al. : Biomarkers of Delirium Duration and Delirium Severity in the ICU. Crit Care Med 2020; 48:353–361 [PubMed: 31770149]

8. Khan BA, Perkins AJ, Campbell NL, et al. : Pharmacological management of delirium in the intensive care unit: A randomized pragmatic clinical trial. J Am Geriatr Soc 2019; 67:1057–1065 [PubMed: 30681720]

9. Ely EW, Margolin R, Francis J, et al. : Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001; 29:1370–1379 [PubMed: 11445689]

10. Khan BA, Perkins AJ, Gao S, et al. : The confusion assessment method for the ICU-7 delirium severity scale: A novel delirium severity instrument for use in the ICU. Crit Care Med 2017; 45:851–857 [PubMed: 28263192]

11. Anthonymuthu TS, Kenny EM, Lamade AM, et al. : Lipidomics detection of brain cardiolipins in plasma is associated with outcome after cardiac arrest. Crit Care Med 2019; 47:e292–e300 [PubMed: 30855329]

12. Gan ZS, Stein SC, Swanson R, et al. : Blood biomarkers for traumatic brain injury: A quantitative assessment of diagnostic and prognostic accuracy. Front Neurol 2019; 10:446 [PubMed: 31105646]

13. Hughes CG, Patel MB, Brummel NE, et al. : Relationships between markers of neurologic and endothelial injury during critical illness and long-term cognitive impairment and disability. Intensive Care Med 2018; 44:345–355 [PubMed: 29523900]

14. Vasilevskis EE, Morandi A, Boehm L, et al. : Delirium and sedation recognition using validated instruments: Reliability of bedside intensive care unit nursing assessments from 2007 to 2010. J Am Geriatr Soc 2011; 59(Suppl 2):S249–255 [PubMed: 22091569]

15. van Eijk MM, van den Boogaard M, van Marum RJ, et al. : Routine use of the confusion assessment method for the intensive care unit: A multicenter study. Am J Respir Crit Care Med 2011; 184:340–344 [PubMed: 21562131]