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NEUROCRITICAL CARE SOCIETY

VIEWPOINT

Delayed reemergence of consciousness in survivors of severe COVID-19

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Survivors of coronavirus disease 2019 (COVID-19) around the world are coming off ventilators every day, having overcome multi-organ system failure and weeks sedated, paralyzed, and isolated from family in the intensive care unit (ICU). The triumph of survival, for those who recover consciousness, is celebrated with nurses, physicians, respiratory therapists and the multitudes of hospital staff who care for patients with COVID-19. The long journey to inpatient rehabilitation, and ultimately home, begins.

Yet many COVID-19 survivors have not recovered consciousness. They remain unresponsive and bedbound, persistently disconnected from their environment. As each day passes after removing the endotracheal tube and weaning sedation, a patient's inability to regain consciousness becomes more disconcerting to families and clinicians. Prolonged alterations of consciousness ranging from coma to delirium have consistently been reported in patients with severe COVID-19 [1–4], but epidemiological estimates of incidence and prevalence are not yet available. Altered consciousness in patients with severe COVID-19 was the most common reason for neurological consultation at our medical centers in New York and Boston during the COVID-19 surge in the Spring of 2020 [5]. Although we tried to use every diagnostic and prognostic tool at our disposal—the neurological exam, electroencephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI)—resource limitations and concerns about the exposure to health care workers and other patients constrained our ability to use these tools. Nearly every question about how severe COVID-19 affects the brain thus remains incompletely answered [6].

Sedation likely contributes to prolonged unconsciousness, given that sustained, high levels of sedation are often needed to ensure ventilator synchrony in COVID-19 patients with acute respiratory distress syndrome (ARDS) [7, 8]. The adverse effects of sedatives on higher-order cognition are well established [9, 10], but how sustained, high doses of sedatives affect the reemergence of consciousness itself is unknown. Moreover, some sedative agents may predispose to more enduring depression of consciousness [11]. After unprecedented drug combinations, dosing regimes, and durations of sedation, often in the setting of hypoxia, metabolic derangements, and impaired drug clearance due to renal or liver failure, the human brain's ability to reintegrate its neural networks is now being tested in ICUs around the world.

Addressing the new challenges posed by the COVID-19 pandemic in a coordinated fashion is likely to inform our understanding of the mechanistic basis of consciousness. As patients emerge from weeks in anesthetic coma, circuits must retune their electrical firing properties; synapses must reestablish their neurotransmitter expression profiles and anatomic specificity [11]. Only with the intricate orchestration of ensembles of networks can the brain regain its full repertoire of integrative cognitive functions. Importantly, recent evidence demonstrates that when brain structure is well preserved (as it is in many slow-to-recover COVID-19 patients), even prolonged coma for several weeks after cardiac arrest may yield independent outcomes [12]. Given uncertainty about the natural history of recovery from COVID-19, it is crucial to better understand the prognostic potential of COVID-19 patients who are slow to recover consciousness.

As the resilience of the human brain is tested by sustained, high levels of sedation, there is also growing recognition that patients with severe COVID-19 are at risk

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for particular forms of brain injury. The pathophysiologic mechanisms of brain injury in severe COVID-19 appear to include hypoxia, inflammation, hypercoagulability [3], endothelial infection by the virus (SARS-CoV-2) [13], and possibly direct infection of the central nervous system by SARS-CoV-2 [14]. The clinical manifestations [1, 3], EEG characteristics [1, 15], CT/MRI findings [3, 16, 17] and histopathological hallmarks [18, 19] of these injurious processes, including elevated stroke risk, are just beginning to be recognized.

As we learn the lessons from the first global wave of COVID-19 and prepare for future battles with this disease, protecting brain function should be at the top of the list of priorities for the medical and research communities. The need for high levels of sedation is compelling in the sickest COVID-19 patients, whose pulmonary function is so tenuous that a single cough could cause ventilator dyssynchrony and hypoxia. But there may be more targeted ways for us to administer sedation and control pain in the ICU [20, 21]—approaches that might also utilize limited resources more effectively.

We need a comprehensive understanding of a critical tradeoff: deeper sedation facilitates treatment of ARDS, but excessive sedation may delay recovery of consciousness and impair neurologic recovery. Ideally, clinicians would use EEG guidance to titrate sedatives to maintain ventilator synchrony while allowing brain function to persist. For example, with propofol, the typical EEG signature of unconsciousness is slow-delta oscillations (0.1–4 Hz) [11]. Hence, the ideal propofol dose would be the one that sustained this pattern at the lowest possible infusion rate. For the majority of COVID-19 patients around the world, even at well-resourced hospitals, it is not feasible to perform continuous EEG monitoring throughout a patient's entire ICU stay. The neurological examination is insufficient for guiding sedative dosing, because comatose patients who are appropriately sedated (e.g. slow-delta oscillations) appear identical on examination to those who are oversedated (e.g. burst suppression). With the duration of sedation approaching weeks, and in some severe COVID-19 patients more than a month [5, 17], long periods of time elapse during which ICU clinicians make well-intentioned decisions about sedation without EEG feedback to guide them.

There is thus an urgent need for a coordinated effort to develop optimized sedation regimens and novel neuroprotective strategies. We must address fundamental gaps in knowledge about how COVID-19 affects the brain, and we need to identify optimal oxygenation thresholds, blood pressure thresholds, and immunomodulatory therapies that might prevent or treat the diverse endotypes of brain injury associated with COVID-19. Patients should have periodic EEG monitoring to prevent prolonged oversedation; the frequency and duration of such monitoring can be determined by local resources and expertise to balance risks to health care workers.

To improve the accuracy of prognostication in patients with disorders of consciousness after severe COVID-19, we need to elucidate the relative utility of EEG, head CT, conventional MRI, and advanced imaging techniques such as functional MRI [17], magnetic resonance spectroscopy [22], and diffusion tensor imaging [23, 24]. Comprehensive safety precautions to protect hospital staff and other patients must be implemented before transporting a patient with severe COVID-19 from the ICU to the MRI scanner. If such safety measures are in place, we support a multimodal approach to prognostication that integrates data from complementary behavioral, electrophysiologic, and imaging tests, consistent with Guidelines endorsed by the American Academy of Neurology, American Congress of Rehabilitation Medicine, National Institute on Disability, Independent Living and Rehabilitation Research [25], and the European Academy of Neurology [26]. Moreover, we recommend that prognoses be based upon the consensus opinion of multidisciplinary specialists with a broad range of expertise [5], including clinicians from neurocritical care, neuroinfectious diseases, epilepsy, neuroradiology, pharmacology, and physical medicine and rehabilitation.

Given the importance of meeting these new challenges with data [27, 28], we applaud recent initiatives to investigate coma recovery by the Neurocritical Care Society's Curing Coma Campaign [29], as well as international initiatives focused on patients with severe COVID-19, such as the Global Consortium Study of Neurological Dysfunction in COVID-19 (GCS-NeuroCOVID) [30], the CoroNerve Study Group [4], and the James S. McDonnell Foundation's COVID-19 Recovery of Consciousness Consortium. These ongoing studies aim to answer four central questions: (1) Which sedation regimens optimize treatment of ARDS but least associate with prolonged disorders of consciousness? (2) What factors cause prolonged impairment of consciousness after severe COVID-19 in the absence of structural brain injuries? (3) Which electrophysiologic and neuroimaging tools differentiate reversible from irreversible causes of altered consciousness? (4) Which patients with disorders of consciousness after severe COVID-19 are likely to recover consciousness, communication, and functional independence? Only with a comprehensive and coordinated international effort can we begin to answer these questions and improve outcomes for patients who survive severe COVID-19.

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