Stressing the Brain: The Immune System, Hypothalamic–Pituitary–Adrenal Axis, and Psychiatric Symptoms in Acute Respiratory Distress Syndrome Survivors

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Advances in critical care medicine have translated into better short-term outcomes for critically ill patients, including reductions in mortality. Although these improvements have led to a growing number of critical illness survivors, including acute respiratory distress syndrome (ARDS) survivors, they have also brought to light the long-term challenges that many survivors face. In addition to burdensome impairments in physical function and cognition (1, 2), many ARDS survivors suffer psychiatric morbidity including depression, anxiety, and posttraumatic stress disorder (PTSD) (3–7).

Unfortunately, two thirds of ARDS survivors suffer impairment in at least one psychiatric domain. The most common pattern involves simultaneous symptoms of depression, anxiety, and PTSD (4, 6). Nearly one in four patients have ongoing PTSD symptoms 1–2 years after their critical illness (4, 6). Despite the enduring effect psychiatric morbidity has on ARDS survivors and their families, research aimed at understanding the underlying mechanisms, discerning potentially modifiable risk factors, and identifying potential therapies is in its infancy.

Although studies have identified younger age, female sex, alcohol abuse, unemployment before illness, and a history of depression as risk factors for subsequent psychiatric impairment, these factors are not modifiable during the acute illness (4, 6, 8). Regarding potentially modifiable risk factors, delusional and adverse memories of intensive care have been linked to the development of PTSD in critical illness survivors (9). To mitigate this risk, the use of a daily intensive care unit diary to improve factual memories has been shown to reduce PTSD symptoms (10).

Despite being a major contributor to delusional memories in critically ill patients, delirium has not consistently been identified as a risk factor for long-term psychiatric impairment (7). Further, exposure to sedating medications during a critical illness have been inconsistently linked to subsequent psychiatric impairment. Higher exposure to benzodiazepines and opioids was associated with increased PTSD symptoms (8) and higher rates of depression, anxiety and PTSD, respectively (6), yet higher-dose opioid exposure was associated with reduced PTSD symptoms in a separate study (5). These discordant results may be related to adequacy of pain control, itself a risk factor for delirium, and not simply a drug effect. Further research is needed to better understand the complex relationships of analgesic and sedative medications with psychiatric outcomes in survivors of critical illness.

One of the few potentially modifiable risk factors identified for psychiatric impairment, and specifically PTSD, in the emerging survivorship literature targets the hypothalamic–pituitary–adrenal (HPA) axis activity. In 1999, based on observational data showing lower circulating cortisol levels in patients with PTSD, Schelling and colleagues examined the potential effectiveness of corticosteroids in a retrospective case-control study of 54 survivors of septic shock. The investigators found that patients treated with stress-dose steroids had a significantly lower prevalence of PTSD (11). In two small, subsequent randomized trials of stress-dose steroids in septic shock and cardiac surgery, corticosteroids led to a lower incidence of PTSD (12, 13). Among 33 ARDS survivors, lower circulating cortisol levels were present in patients with traumatic memories of their intensive care unit course, and greater exposure to corticosteroids during critical illness was associated with fewer PTSD symptoms (5, 14). Last, among 42 lung transplant recipients, each conditioned with high-dose steroids perioperatively and maintained thereafter on prednisone, a startling 0% of survivors experienced PTSD (15).

In this month's issue of the *AnnalsATS*, Spencer-Segal and colleagues (pp. 960–967) add to the growing evidence linking the immune system and HPA axis with psychiatric symptoms in survivors of critical illness (16). As part of a multicenter, randomized, placebo-controlled trial of granulocyte macrophage-colony stimulating factor (GM-CSF) in acute lung injury, patients completed several validated assessments for psychiatric symptoms at their 6-month follow-up visit. The Hospital Anxiety and Depression Scale (HADS) was

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used to assess for symptoms of depression and anxiety, and the Post-traumatic Stress Syndrome 10 Questions Inventory (PTSS-10) and Impact of Events Scale (IES) were both used to assess for posttraumatic stress symptoms.

Of the 132 patients enrolled, 98 survived and 44 (45%) survivors completed at least one psychiatric assessment. Corticosteroid treatment was not protocolized, and 22 patients (50%) received steroids during their ICU course. Between 20% and 25% of survivors had significant PTSD symptoms at 6 months, depending on the scale used, whereas 14% had significant depressive symptoms and 18% had significant anxiety symptoms. In adjusted analyses, patients in the GM-CSF treated group had higher scores (higher burden of psychiatric symptoms) on all four assessments, although the scores were only significantly higher for the HADS-depression and PTSS-10 assessments.

Consistent with prior studies, younger age was associated with higher symptom scores on both PTSD scales as well as the HADS-anxiety scale, and female sex was associated with higher IES scores. More days of steroid treatment were also found to be associated with significantly lower HADS-anxiety and IES scores.

To explore the relationship between GM-CSF, the HPA axis, and psychiatric symptoms, the authors measured plasma cortisol approximately halfway through the 14-day GM-CSF protocol (treatment day 7–10) in patients who did not receive steroid treatment at any point during their ICU stay. Although not statistically significant, the mean plasma cortisol concentration was lower in GM-CSF-treated patients (19.7 vs. 29.6 μg/dL; $P = 0.12$), and lower cortisol concentrations appeared to correlate with higher symptom scores.

Although many of the findings in this small study did not meet statistical significance, the direction of the associations are consistent with prior studies. As a result, the findings add support to a potential link of lower circulating cortisol with psychiatric symptoms and increased exposure to corticosteroids with fewer psychiatric symptoms. Through the process, GM-CSF, postulated to improve ARDS by preventing alveolar epithelial injury and stabilizing alveolar macrophage function (17), may be another example of an intervention that has real or theoretical benefits in the short term, yet paradoxically, have long-term consequences (e.g., neuromuscular blocking agents and long-term neuromuscular dysfunction) (18). Adding further complexity, corticosteroids may be associated with the development of long-term physical impairment (19), and thus the same intervention could be beneficial and harmful in the long term to different functional domains.

Although this study is strengthened by the use of well-validated assessments for psychiatric symptoms, by the sound analytic methodology, and by leveraging a clinical trial, some limitations are noteworthy. There was substantial loss to postdischarge follow-up, with only 45% of survivors completing at least one psychiatric assessment at 6 months. Also, psychiatric outcomes were not the primary endpoints of the original clinical trial, and thus the current, *post hoc* study was underpowered, most notably in regard to cortisol measurements, which were completed in only 16 patients. In addition, plasma cortisol concentrations were measured at a single point, which may not capture the full relationship between the HPA axis and psychiatric symptoms.

In conclusion, the study by Spencer-Segal and colleagues is an important contribution to the survivorship literature, and one that adds further support to the hypothesis that immune activity and the HPA axis play a role in the development of psychiatric morbidity in critical illness survivors (16). Given the prevalence and the profound effect of depression, anxiety, and PTSD in critical illness survivors, future research is desperately needed to elucidate how the immune system and HPA axis interact with the brain, and whether or not this interaction can be therapeutically targeted. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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