Covert Critical Illness Encephalopathy: Impairments That Escape Detection by Guideline Recommended, Protocolized Assessments

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OBJECTIVES: To determine whether cognitive impairments of important severity escape detection by guideline-recommended delirium and encephalopathy screening instruments in critically ill patients.

DESIGN: Cross-sectional study with random patient sampling.

SETTING: ICUs of a large referral hospital with protocols implementing the Society of Critical Care Medicine's ICU Liberation Bundle.

PATIENTS: Patients with a heterogeneous mix of primary organ system conditions leading to critical illness and with no abnormal findings scored in Confusion Assessment Method for the ICU (CAM-ICU) screening, Richmond Agitation-Sedation Scale (RASS) 0, and Glasgow Coma Scale (GCS) 15, indicating they were alert, fully oriented, and following commands with no delirium or findings to indicate subsyndromal delirium.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We evaluated 50 patients, age 54 ± 16 years. Trained critical care nurses assessed patients at regular intervals using the CAM-ICU, RASS, and GCS per a protocol. We performed a battery of psychometric cognitive tests using the NIH Toolbox. Executive functions linked to attention and inhibitory control, and processing speed were 1.5 SD below population norm (both $p < 0.01$). Working memory and cognitive flexibility were also significantly, but less severely, impaired ($p < 0.01$ and $p = 0.026$). Nearly two-thirds (64%) of the patients scored at least 1.5 SD worse than demographically adjusted means in two or more cognitive domains, a commonly used diagnostic criterion for cognitive impairment.

CONCLUSIONS: Substantial cognitive impairment is present among critically ill patients with no abnormalities detected by standard delirium and encephalopathy assessments.

KEYWORDS: cognition; critical illness; delirium; encephalopathy

During critical illness, the organ failure syndrome of the CNS manifests as encephalopathy, with its severity ranging from subsyndromal delirium to coma. Delirium occurs in at least half of critically ill patients and is an independent predictor of mortality and chronic cognitive impairments (1, 2). Subsyndromal delirium, in which patients have some abnormal findings on a delirium screening instrument but below the complete diagnostic threshold, is associated with adverse cognitive outcomes, suggesting the morbidity of mild encephalopathy (3).

In patients with liver cirrhosis, covert hepatic encephalopathy, missed by routine assessment instruments and only recognizable by psychometric testing, is now established as clinically important, influencing quality of life, socioeconomic status, risk of driving accidents, falls, progression to overt hepatic

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KEY POINTS

Question: Do clinically important cognitive impairments escape detection by guideline recommended, protocolized assessments for delirium and encephalopathy in critically ill patients?

Findings: We performed a battery of psychometric tests in critically ill patients who demonstrated no abnormal findings on the Glasgow Coma Scale, the Richmond Agitation Sedation Scale, or the Confusion Assessment Method for the ICU. Nearly two-thirds of the patients scored at least 1.5 SDs worse than demographically adjusted means in two or more cognitive domains, a standard diagnostic threshold for clinically important impairment.

Meaning: Substantial cognitive impairments in critically ill patients may routinely escape detection.

encephalopathy, and death (4). Whether important cognitive impairments in critically ill patients escape detection by common mental status assessments and delirium screening instruments is unknown. The objective of this study was to investigate the presence and degree of covert encephalopathy among a diverse sample of critically ill patients with no impairments identified by standard delirium and encephalopathy screening.

METHODS

Patients

The study was approved by the Northwestern University Institutional Review Board (Actigraphy in the Critically Ill; STU00203802; August 31, 2016) and written informed consent was obtained from participants. Study procedures conformed with the ethical standards of the institutional review board and with the Helsinki Declaration of 1975. We enrolled patients by random convenience sampling, approaching cases in all ICUs meeting inclusion and exclusion criteria on days when study staff was available. Inclusion criteria were: 1) age 18 years old or older, 2) critical illness, which we defined as a state of ill health with vital organ dysfunction requiring intensive care to manage the high risk for death or severe permanent injury, and 3) absence of delirium and/or abnormal findings on delirium screening items indicative of subsyndromal delirium or other mental status changes as confirmed by negative findings on all tested elements of the Confusion Assessment Method for the ICU (CAM-ICU), Richmond Agitation-Sedation Scale (RASS) score 0, and Glasgow Coma Scale (GCS) score 15, with all assessments performed by trained critical care nurses. Training for critical care nurses comprised a standardized didactic session to review the purpose and contents of the assessments followed by multiple supervised administrations of each assessment in the presence of designated nurse preceptors to confirm competency. Exclusion criteria were: 1) cases admitted to intensive care for high intensity postoperative care, frequent monitoring or related complex nursing demands but without critical illness, 2) cases identified by the clinical team as possibly or definitely ready to transfer to an intermediate care unit or floor status that day, and 3) inability to speak English as required for psychometric testing with NIH Toolbox. All patient care units had implemented the Society of Critical Care Medicine's ICU Liberation Bundle. A board-certified neurologist (M.B.M.) reviewed the admission history, medications, and historical and currently assigned diagnoses for identifiers of cognitive impairment and/or dementia, consistent with methods used to assess delirium instruments and the health record based approach favoring sensitivity (5, 6). Cases with a chronic neurologic condition, excluding sleep disorders, primary headache disorders and conditions only affecting the spinal cord or peripheral nervous system, underwent a second-level review of prior ambulatory records, when available, to screen thoroughly for condition-associated evidence of cognitive impairments.

The CAM-ICU is a diagnostic instrument for delirium with 95–96% sensitivity for diagnosis of delirium in critically ill patients when administered by trained nurses (6). Many delirium instruments, including the CAM-ICU, employ sequenced logic that does not require all items to be scored to complete an assessment. Subsyndromal delirium is commonly defined as the presence of abnormal findings on a delirium-testing instrument below the qualifying threshold for delirium. The RASS is a validated instrument for assessing agitation and reduced alertness, often used to adjust medications for agitation management or sedation. A RASS score 0 indicates a patient is alert

TABLE 1.
Patient Characteristics

Characteristic	
Participants (*n*)	50
Female (%)	30 (60)
Age, mean ± SD, range	54 ± 16, range 21–88 yr
Primary organ system failure (%)	
Cardiovascular	10 (20)
Gastrointestinal/digestive	12 (24)
Metabolic derangements (endocrine, renal)	6 (12)
Neurologic	1 (2)
Respiratory	21 (42)
Mechanical ventilation (%)	0 (0)
Vasopressors (%)	19 (38)
Sepsis (%)	18 (36)
IV sedatives (%)	1 (2)
Sequential Organ Failure Assessment score, median (interquartile range), range	3 (2–5.75), range 0–12
Duration of hospitalization on date of assessment, median (interquartile range), range	3 (1–10.75), range 0–65 d

and calm. The GCS is a validated scale used to assess impairment in alertness and consciousness and has shown high reliability and reproducibility among critically ill patients. A GCS score 15 indicates a patient is alert with eyes open spontaneously, oriented and obeying commands. The frequency of these assessments at our institution is bid for the CAM-ICU and every 4 hours for the RASS and GCS.

Cognitive Evaluation

Psychometric cognitive testing was performed with NIH Toolbox using the Flanker Inhibitory Control and Attention Test to assess selective attention and inhibitory control aspects of executive functioning, the List Sorting Working Memory Test to assess working memory function, and the Pattern Comparison Processing Speed Test to assess processing speed, as we have previously described (7, 8). We administered the Dimensional Change Card Sort Test, an assessment of the cognitive flexibility aspect of executive functioning, in a subset of patients. We have previously reported that some acutely ill patients are unable to complete a testing battery despite initial willingness to participate so we initiated testing with the Flanker test, hypothesizing it would be most likely to show abnormalities and thus highest priority for data collection (8). Cognitive testing was performed by certified study staff who underwent training consistent with the NIH Toolbox Administration Guidance and Administrator's Manual including online modules, in-person training, preceptored administration, and a credentialing process through the Northwestern Medicine healthcare system. NIH Toolbox test results are reported as T scores, in which 50 is the reference population mean and 10 is the SD. We used fully corrected T scores that were adjusted for age, gender, race/ethnicity, and education. Higher scores for NIH Toolbox tests indicate better cognitive function.

Statistical Analyses

We used *t* tests to compare NIH Toolbox T scores to the demographically adjusted population norms and reported the proportion of patients whose cognitive performance scores were 1.5 SDs below population means, a common threshold to define clinically significant cognitive impairment (9). Statistical analyses were performed in R, Version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We assessed 50 critically ill patients, 30 female and 20 male, mean age 54 ± 16 years, ranging from 21 to 88

TABLE 2.
Cognitive Testing Results Among Critically Ill Patients With No Delirium or Other Mental Status Changes on Standard Screening Tests

Cognitive Test	No. Completed	Mean ± SD	% < 1.5 SD Below Population Mean	*p* vs. Population Norms
Flanker inhibitory control and attention test	50 (100%)	36 ± 10	56%	< 0.01
Pattern comparison processing speed test	49 (98%)	36 ± 12	63%	< 0.01
List sorting working memory test	43 (86%)	45 ± 11	21%	< 0.01
Dimensional change card sort test	21 (72%)[a]	45 ± 10	19%	0.026

[a]Testing attempted with 29 participants.

years old. Patient characteristics are detailed in **Table 1**. The primary organ system failure leading to critical illness was respiratory in 21 (42%), gastrointestinal/digestive in 12 (24%), cardiovascular in 10 (20%), metabolic in 6 (12%), and neurologic in 1 (2%). One patient had received an IV sedative within five half-lives: a 1 mg dose of lorazepam 5 hours before assessment. Two other patients had received hydromorphone at analgesic dosing. No patient had evidence of existing cognitive impairments by medical history, medication record, or coded diagnoses. The following chronic neurologic conditions were present, but without evidence of comorbid chronic cognitive impairment: cerebral aneurysm, epilepsy, neuromyelitis optica, fibromyalgia, four cases of stroke without residual deficits, and prior hepatic encephalopathy without pre-hospitalization symptoms or active treatment. Consistent with inclusion criteria, all patients had negative CAM-ICU for delirium, GCS 15, and RASS 0 on the assessments immediately before cognitive testing. At the next routine nursing assessment after cognitive testing, CAM-ICU remained negative and GCS scores remained 15 in all patients, RASS remained 0 in 47 (94%) and changed to –1 (drowsy) in 3 (6%).

The median time from admission to assessment was 3 days (interquartile range [IQR], 1–10.75 d). Cognitive performance was significantly below demographically adjusted population norms (**Table 2**). By study design, Flanker test results were obtained in all subjects. All but one subject completed the Pattern Comparison Processing Speed test. The test completion rate was lower for tests administered later in the examination battery. Flanker scores were not significantly different between subjects who completed all testing and those who did not (mean 37 ± 10 vs. 34 ± 9; $p = 0.28$).

Executive functions linked to attention and inhibitory control, and processing speed were more severely abnormal, mean 1.4 SD below population norm ($p < 0.01$). Working memory and cognitive flexibility were also significantly, but less severely, impaired. Using 1.5 SDs below the expected population mean as a diagnostic threshold to confirm cognitive impairment, domain-specific impairment ranged from 19% to 63%, with 64% of subjects found to be impaired in at least two domains. We found a modest correlation between scores on the Flanker test and the Pattern Comparison test (correlation, 0.37; $p < 0.01$) and Dimensional Change test (correlation, 0.52; $p = 0.015$), and none between the other cognitive tests. We found no significant difference in cognitive performance by vasopressor use, presence of sepsis, or a correlation with Sequential Organ Failure Assessment (SOFA) score.

DISCUSSION

In a representative sample of critically ill patients who scored negative by guideline-recommended, validated methods of identifying delirium or encephalopathy, we found that the majority are cognitively impaired according to psychometric testing standards. These findings indicate that covert critical illness encephalopathy may be common and underrecognized. Neurologic assessment instruments commonly used in critical care, such as the CAM-ICU, RASS, and GCS, exhibited psychometric ceiling effects at moderate severity cognitive impairment and were insensitive to impairments of lesser, but potentially consequential, severity.

We previously reported extensive cognitive impairments among critical illness survivors near the time of hospital discharge, along with psychometric ceiling effects of the GCS and CAM (8). The findings we report here extend those observations to critically ill patients and confirm that covert encephalopathy is

widespread among those without delirium or more severe encephalopathy. The population of critically ill patients represented by this sample is large: nearly 40% of critically ill patients remain at maximum GCS score throughout the initial 24 hours of resuscitation and stabilization, and the GCS score compresses further to the scale ceiling as patients physiologically stabilize (10). The disease severity of patients in this sample (median SOFA 3 [IQR, 2–5.75]) is only modestly less than what is found in a typical ICU, for example, the 111,885 patients in the electronic ICU Collaborative Research Database (median SOFA 4 [2–6]) (11). The occurrence rate of delirium varies by study, but a meta-analysis of modern studies including a broad sample of patients, most of which were assessed by the CAM-ICU, estimates that delirium is identified in only 32% during their intensive care stay (12). Many critically ill patients, thus, are not recognized as neurologically impaired.

While much attention has been paid to the association between ICU delirium and worse cognitive outcomes, the long-term cognitive function of patients who experience no delirium during hospitalization is also markedly worse than population means, and the effect attributable to delirium accounts for less than half the difference (2). Covert encephalopathy may account for some of the cognitive morbidity of critical illness among patients with a low delirium burden.

Our study has limitations. Our referral center patient population may not be generalizable to all critically ill patients. Measurement errors may have yielded false negative test findings, but the GCS, RASS, and CAM-ICU have shown excellent sensitivity and reliability and their implementation at our institution represents best practice, supporting generalizability. The CAM-ICU employed sequenced logic, potentially limiting the characterization of subsyndromal delirium. We have previously shown that many patients tire during brief cognitive testing and do not complete assessments (8). We deferred additional assessments to evaluate alternative instruments or retesting individual items to avoid drop out of patients that would bias results, but exploring detection sensitivity other bedside assessment methods would be an important future study. As research has demonstrated the consequences of similar impairments in patients with liver disease, the term covert has replaced descriptors like minimal, latent, or subclinical encephalopathy, which trivialize the condition. Studies validating delirium assessments excluded major neurologic conditions and severe dementia. We used similar methods, but nevertheless the cross-sectional approach used in this study cannot support firm inferences as to whether cognitive deficits are acute or chronic. The CAM-ICU, used here, included the determination that the patient's mental status is not different from pre-hospitalization baseline. Further studies will be needed to determine whether covert critical illness encephalopathy is associated with medical complications and cognitive outcomes.

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Dr. Maas designed the project. Ms. Shirodkar, Dr. Bourgeois, and Dr. Maas acquired the data. Dr. Maas performed the analyses. Ms. Shirodkar and Dr. Maas wrote the article text. All authors contributed to the interpretation of data and substantially revised the article.

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