Chapter 8
Delirium After Primary Neurological Injury

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Introduction

Over the last two decades, delirium has been identified as a major morbidity of critical illness leading to increased hospital length of stay, ICU days, mortality, and long-term cognitive impairment with loss of independence and quality of life [1–4]. Much of delirium research has been repeatedly validated in medical, surgical, and cardiovascular critical care patients. Delirium metrics, however, are not as widely applied in patients with acute primary brain dysfunction, also known as primary neurologic injury (PNI) related to stroke (ischemic and hemorrhagic) or traumatic brain injury (TBI) [2, 5–7].

Until recent years, the limited investigations and application of delirium in PNI are likely rooted in the assumption that delirium cannot be assessed in these patients. PNI can result in permanent structural injury to the brain leading to lifelong changes in cognition, language, perception, motor ability, and sensorium. These acute changes can make delineating secondary cerebral dysfunction, such as delirium, from the primary injury very difficult. However, a growing number of studies have shown delirium assessment in neurologically injured patients is possible and that delirium after PNI has similar poor outcomes compared to non-PNI cohorts.

In this chapter, we hope to better clarify the existing data on prevalence and outcomes of delirium in PNI patients. Further, we hope to provide a platform for future studies and delineate what is still not understood from the available literature.

Delirium Assessment in Primary Brain Injury

Even after PNI, delirium assessment is still based on four main criteria (i.e., acute onset with fluctuating course, inattention, disorganized thinking, altered level of consciousness) derived from the Diagnostic and Statistical Manual of Mental Disorders version IIIR (DSM-IIIR), DSM-IV, and more recently DSM-V. In patients with PNI, Inouye's Confusion Assessment Method (CAM) [8] has been studied, as has Ely's Confusion Assessment Method for ICU (CAM-ICU) [9]. The CAM-ICU utilizes the Richmond Agitation-Sedation Scale (RASS) as part of its assessment for consciousness. Patients with coma (RASS scores of −4 and −5) are unable to be assessed for delirium with the CAM-ICU. This challenge exists for many patients with severe PNI, as they often start and/or progress to a comatose state.

Other assessment methods have been used in patients with PNI, including the Intensive Care Delirium Screening Checklist (ICDSC) [10, 11] and the 4-A Test (4AT) rapid clinical test for delirium [12, 13]. We note that there are currently no delirium assessment tools that are specifically tailored toward patients with PNI.

Assessment of delirium in patients with PNI has been performed less universally than in other critically ill patient cohorts. Elements contributing to this difference

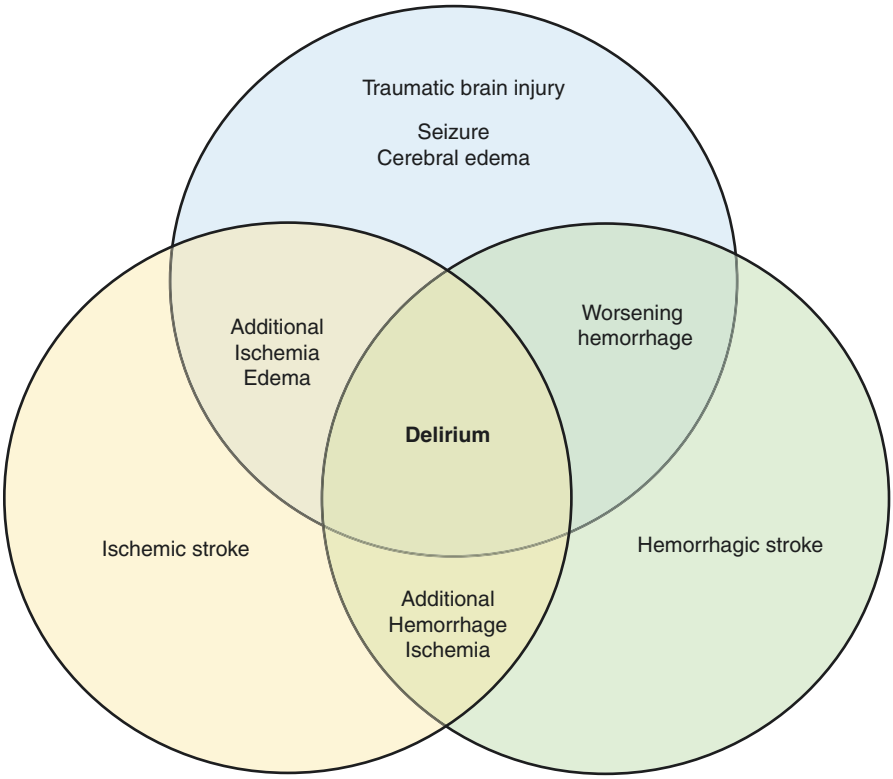

Fig. 8.1 Differential diagnoses for mental status change in the neurologically injured

include comatose state, unclear neurologic baselines after PNI, and communication difficulties such as aphasia limiting ability for interactive assessment. Most importantly, acute mental status changes in patients with PNI must first be assessed for acute processes such as further ischemia, cerebral edema, hemorrhage, seizures, or encephalitis (Fig. 8.1). Once these have been ruled out, additional sources of changes of mental status from new baseline are relevant to delirium measurement.

Review of the Primary Literature

Building on a recent systematic review on delirium in neurologically injured patients [14], we hope to further detail the primary literature on the evaluation of delirium in patients with PNI. We specifically focus on delirium findings as it relates to three subcategories of neurologic injury: TBI, intracerebral hemorrhage, and ischemic stroke.

Traumatic Brain Injury

TBI, defined as an alteration in brain function caused by an external force, is a major public health concern, with an incidence exceeding two million individuals annually in the USA alone [15]. Only two studies were identified in the most recent literature on the evaluation of delirium in a TBI population. These studies both confirm the ability to assess delirium in individuals with TBI.

The first is a 2008 retrospective review by Scherer et al. of 132 patients admitted to an inpatient brain injury neurorehabilitation unit post-hospital discharge from an acute hospital admission for TBI [16]. Individuals with confusion while in rehabilitation had worse clinical and long-term outcomes. Using their own internally validated Confusion Assessment Protocol, the authors noted a longer acute hospital length of stay in patients with delirium. Employability and productivity status at 1-year post-injury for discharged patients who survived, the primary outcomes for this study, were lower in individuals who experienced longer confusion times.

A second study sought to validate screening tests for delirium in a TBI population. In a 2016 prospective study of patients with mild to moderate TBI admitted to an ICU following multisystem trauma, Frenette et al. assessed patients at three separate time points during the ICU hospitalization for delirium with the CAM-ICU, the ICDSC, and psychiatric evaluation using the DSM-IV-TR [17]. Compared to the DSM-IV-TR gold standard, CAM-ICU and ICDSC had sensitivities of 62 and 64%, specificities of 74 and 79%, and good inter-rater reliability (kappa 0.64 and 0.68), respectively. Both assessments had similar positive predictive values (63 vs 74%) and negative predictive values (70 vs 69%). Of note, the assessment of delirium with CAM-ICU and ICDSC assessments in the second study was done by pharmacists and then compared to the assessment of intensivists and psychiatrists. Although in clinical practice these assessments are traditionally completed by bedside nurses, the high inter-rater reliability again demonstrates the capability of a wide range of providers to administer these tests.

Overall there is a paucity of data describing delirium in the TBI population. The INSIGHT-ICU (Illuminating Neuropsychological dysfunction and Systemic Inflammatory mechanisms Gleaned after Hospitalization in Trauma-ICU Study, clinicaltrials.gov NCT03098459) [18] is an accruing prospective cohort of critically ill trauma patients, which will better define the impact of delirium in trauma ICU patients with and without TBI.

Hemorrhagic Stroke

Nontraumatic intracerebral hemorrhage, (ICH) or hemorrhagic stroke, affects approximately 100,000 new individuals per year in the USA [19]. The following studies show that delirium can be adequately assessed in individuals with nontraumatic ICH and that delirium after this form of PNI is associated with worse long-term outcomes.

In a 2013 study by Naidech et al., patients (n = 114) with nontraumatic hemorrhagic stroke in the ICU were assessed twice daily for delirium via the CAM-ICU by bedside nurses [20]. Delirium prevalence was 27%, and symptoms were nearly always hypoactive rather than hyperactive. The presence of delirium led to a statistically significant increase in both ICU and hospital length of stay even after controlling for patient age, benzodiazepine use, and admission National Institute of Health Stroke Scale (NIHSS). Delirium was also associated with worse quality of life, poor executive function, and decreased cognition at 1-year assessments even after adjusting for other factors. Of note, this population had lower reported baseline levels of dementia than other stroke populations.

In 2017, Rosenthal et al. examined another prospective cohort of patients with spontaneous nontraumatic ICH (n = 174), with 30% of patients developing delirium, as assessed twice daily by trained nursing staff using the CAM-ICU [21]. Patients with delirium had worse cognitive function and quality of life at 28-days and 1-year post-hospital discharge even after controlling for severity of neurologic injury, age, and time of assessment. There was no documented association between medication or infection and delirium. They also noted a close association of delirium with agitation (as assessed by the RASS) in this hemorrhagic stroke population and worse outcomes in those with documented delirium and agitation. This study, like others, excluded individuals with severe ICH as they were unable to be assessed due to coma.

Ischemic Stroke

There are approximately 700,000 individuals affected by cerebrovascular accident, or ischemic stroke, annually in the USA. Combined with the aforementioned ICH, stroke is the fifth leading cause of death in the USA [19]. Assessing delirium in this population has been documented in a larger number of studies than other PNI populations. Six studies documented an 11.8–43% prevalence of delirium in the ischemic stroke population (sometimes admixed with hemorrhagic stroke). A number of delirium risk factors were identified, including age, stroke severity, and certain stroke characteristics [22–27]. Delirium was also associated with worse outcomes in this stroke population [22, 24, 26].

In a 2011 study, patients admitted to a Netherlands stroke unit (n = 527) were assessed for delirium via CAM at two separate time points in the hospitalization, reporting an 11.8% overall prevalence [22]. Oldenbeuving et al. attributed the low delirium prevalence to the limited time frame for assessment (two time points vs multiple daily assessments) given that acute onset and fluctuating course is a hallmark delirium feature. Risk factors for delirium included pre-stroke cognitive decline, infection, higher NIHSS, and brain atrophy. Delirium was independently associated with higher length of stay and worse functional outcomes but not with mortality.

In a 2012 study by Kostalova et al., patients (n = 119) with either ischemic or hemorrhagic stroke admitted to an ICU were followed up to 1 week [23]. Daily

delirium assessments were completed by trained professionals using DSM-IV criteria and CAM-ICU. Delirium prevalence was 43%, with 67% of cases within the first 24 h of poststroke admission. Onset of delirium occurred within the first 5 days of stroke onset, with a median duration of 5 days. Risk factors for delirium included increasing age, suspected or diagnosed pre-stroke dementia, lab markers associated with chronic alcoholism (elevated gamma-glutamyl transferase and thrombocytopenia), and increased severity of illness via metabolic derangements (hyponatremia, creatinine, hyperbilirubinemia). Stroke characteristics associated with increased delirium risk were hemorrhagic stroke, large ischemic volume (>40 cm^3), and large hemispheric infarctions (total anterior circulation infarction).

Also in 2012, Mitasova et al. reported a delirium prevalence of 24% with daily CAM-ICU assessment in patients with either ischemic or hemorrhagic stroke evaluated in the ICU for 1 week post-event ($n = 129$) [24]. As compared to the study era's DSM-IV gold standard, the CAM-ICU assessment in this population demonstrated high sensitivity and specificity (76% and 98%), accuracy (94%), and inter-rater reliability (kappa 0.94). Delirium in this poststroke population was independently associated with longer hospital length of stay, even after adjusting for other clinical factors (e.g., age, gender, prestrike dementia, NIHSS on admission, severity of illness score, aphasia). Patients with stroke and delirium had worse functional status than non-delirious stroke patients, but delirium was not an independent risk factor for mortality after adjusting for clinical characteristics.

In 2013, Lees et al. assessed patients ($n = 111$) with acute stroke for delirium at one time point between day 1 and 4 post admission to a dedicated stroke unit with a variety of screening tests [25]. This sample population, which excluded individuals with severe stroke, included a high prevalence of individuals with pre-stroke dementia (41%) as assessed by the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and high levels of cognitive impairment as assessed by Montreal Cognitive Assessment (MoCA), up to 85% using the most sensitive cutoff (MoCA <26). Using the CAM assessment as the reference standard, the 4AT test demonstrated high sensitivity (1.0, 95% CI [0.74–1.0]) and specificity (0.82, 95% CI [0.72–0.89]) for delirium detection. Abbreviated mental tests (AMT-10 and AMT-4) had lower sensitivity (0.75, 0.83) and specificity (0.61, 0.61) for delirium detection.

In a 2018 prospective cohort study, patients ($n = 261$) admitted with initial or recurrent ischemic stroke were assessed for delirium using CAM assessments at two different times during their first hospital week, with a reported 14.6% delirium prevalence [26]. Of note, Qu et al. excluded preexisting cognitive disorders such as dementia. Risk factors for delirium were increased age, higher NIHSS at admission, and prior stroke. Stroke-specific characteristics that were predictors of delirium included left cortical infarcts, larger infarct volume, and more severe medial temporal lobe atrophy – all of which are also associated with advanced age. A smaller number of patients with and without poststroke delirium were assessed at 3 and 6 months. Poststroke delirious patients ($n = 38$) showed trends toward worse functional outcomes, but this was not statistically significant likely due to small sample size.

A 2018 study by Pasinska et al. assessed patients ($n = 750$) admitted with ischemic or hemorrhagic stroke with the abbreviated CAM (bCAM) or CAM-ICU [27]. Prevalence of delirium was 27% with hypoactive and mixed subtype being the most common (41.9% and 39.9%, respectively), while a small number developed hyperactive delirium (15.3%). Independent risk factors for delirium that were identified included pre-stroke mental status, cumulative illness rating score, and admission cognitive dysfunction (MoCA score). Elevated white blood cell count and urinary tract infection during admission were risk factors for developing delirium. Of note, right-sided lesions were more suggestive of future delirium with a trend toward significance.

Discussion

A review of the literature emphasizes that delirium after PNI is a clinically relevant phenomenon and deserves further scientific inquiry. From the available studies, delirium after PNI likely has an impact on functional outcomes but with an unclear impact on mortality. The lack of association of delirium after PNI with survival may be related to the use of improved biostatistical techniques and covariate adjustment. Common risk factors that may potentiate delirium included pre-stroke dementia or functional impairment, age, medical comorbidities, degree of neurologic impairment after stroke (NIHSS scores), and certain anatomic areas of injury.

Individuals with PNI have a unique risk for delirium, as there are actual structural disturbances within the brain, compared to other critically ill populations without PNI. Several of these studies remarked on structural components as possible risk factors for delirium [21–23, 26, 27]. The larger prospective studies evaluating a poststroke population, such as those by Qu et al. [26], Pasinska et al. [27], and Oldenbeuving et al. [22], were the most robust investigations on the structural components of poststroke delirium. Separately identified in these different studies, regions of the brain that have potentially increased delirium risk when injured include parahippocampal regions [21], anterior circulation strokes [22, 23], and both right [21, 22, 27] and left [26] hemisphere strokes. One explanation for these variable findings is that any larger insult may facilitate either profound language and cognitive deficits or visuospatial abnormalities, such as hemineglect that may either promote delirium and/or make it more difficult to diagnose in light of our current delirium assessment methods being dependent on language production, comprehension, and visuospatial reasoning. Kostalova et al. alluded to these suggestions and showed that the volume of brain injured correlated with risk of delirium development [23].

The primary structural insult in these patients, differing them from other critically ill cohorts, creates a perpetual confounder, as it can be unclear whether the clinical constellation we evaluate is a result of this underlying structural abnormality, as opposed to true secondary brain dysfunction of delirium caused by infectious, metabolic, and/or hypoxic reasons. As always, delirium must be a diagnosis of exclusion after other life-threatening PNI-related causes of altered mental status are considered (Fig. 8.1).

An important item to note in the assessment of delirium in PNI is the establishment of a "new baseline." This was explicitly mentioned in two works from the same group [23, 24] on the evaluation of patients with stroke. These patients were evaluated on admission for a "new baseline." This baseline was adjusted upward if their mental status improved to its pre-hospital state, but otherwise delirium was identified with fluctuations in mental status from this new post-PNI baseline, not from what is considered "normal" or pre-PNI.

Another important factor affecting the bedside assessment of delirium is the impact of aphasia or communication deficits after PNI. Mitasova et al. noted false-positive assessments of delirium with the CAM-ICU, as compared to DSM-IV, due to underlying global or receptive (i.e., Wernicke's) aphasia [24]. Assessment of delirium with bedside tests in this subset of patients must take into account the patient's ability to understand verbal or written instructions and respond to visual, auditory, or tactile stimuli. Further work is needed in this realm for better rapid delirium assessments in the aphasic or sensory-deprived PNI patient population.

Conclusion

The current literature on delirium after PNI is not as robust as that for other critically ill patients, but the emerging literature suggests similar findings to non-neurologically injured delirium cohorts hailing from medical and/or surgical ICUs. Delirium is measurable after PNI with reasonable test characteristics for a number of delirium assessment tools. After PNI, there is a significant impact of delirium on hospital and ICU length of stay, as well as cognitive and functional outcomes, but delirium's impact on mortality in PNI has yet to be properly established [14]. The best data are in poststroke delirium, with a significant paucity of large prospective studies in patients with TBI. The INSIGHT-ICU Study is an accruing prospective cohort that will better define the impact of delirium in a critically ill trauma cohort with and without TBI [18]. Further work needs to be done both on confirming the outcomes of delirium and potentially different subsets of risk factors in patients with PNI, as well as the development of delirium assessment methods tailored to patients with altered language processing and visuospatial deficits from their underlying brain injury.

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