NEUROLOGIC COMPLICATIONS OF CRITICAL CARE

Christopher Kramer, MD

Introduction:

Significant improvements have been made with regard to mortality in patients with sepsis and critical illness over the last decade. However, this success is mitigated by the fact that 60-80% of critically ill patients will become delirious during their hospital stay, 50-70% will suffer cognitive impairment after discharge, and 60-80% will have physical disability due to ICU acquired weakness. Furthermore, survivors of critical illness are five times more likely to develop depression after discharge and up to 25% will experience symptoms of post-traumatic stress disorder (PTSD). These staggering figures underscore the need to better understand and treat these common neurologic complications of critical care that can significantly and adversely affect the quality of life of these patients. In this course, we will review each of the respective conditions—ICU acquired weakness, delirium and associated long-term cognitive impairment, and neuropsychological disorders related to critical illness.

ICU Acquired Weakness:

ICU-acquired weakness (ICUAW) has been defined as a “syndrome of generalized limb weakness that develops while the patient is critically ill and for which there is no alternative explanation other than the illness itself.” It has been objectively defined by a summated score of less than 48 on the medical research council (MRC) scale during an abbreviated and standardized neurological examination in the context of critical illness. Critical illness neuromyopathy (CINM), a term encompassing the common co-occurrence of critical illness myopathy (CIM) and critical illness polyneuropathy (CIP), is the most common cause. Muscle atrophy due to immobilization and the catabolic conditions inherent in the setting of critical illness is another entity that likely also contributes to ICUAW and may co-occur with CINM.

ICUAW is extremely common—its incidence can approach 56% - 80% of patients depending on risk factors and timing. Such risk factors include the systemic inflammatory response syndrome (SIRS)/sepsis, multi-organ failure, and hyperglycemia. The use of corticosteroids and paralytics have not consistently been reported as risk factors, particularly in adjusted studies. Pathologically, CIP is a length-dependent sensorimotor polyneuropathy and CIM is a myopathy characterized by thick filament loss representing myosin breakdown. Functionally, a sodium channelopathy in CIM results in inexcitable muscle tissue. The downstream effects of inflammation, including slowing and obstruction of microvascular flow, increased diffusion distance due to tissue edema, tissue damage from circulating toxins, and mitochondrial injury is suspected to be the primary mechanism.

ICUAW/CINM most commonly manifests as a flaccid quadriparesis and respiratory weakness that may result in failure to wean from mechanical ventilation despite normal gas exchange. Symptom manifestation can be obscured by encephalopathy, sedation, and/or pharmacologic paralysis and can occur suddenly and within a few days of ICU admission. Clinical hallmarks of CIM include distal weakness, sensory loss, and areflexia, with sparing of the facial and extraocular muscles. In contrast, weakness in CIM is typically proximal, can involve the face and, rarely, the extraocular muscles. No sensory loss occurs in CIM and deep tendon reflexes are relatively preserved. Recent evidence also suggests that small fiber neuropathy and autonomic dysfunction can occur in CINM, though confirmatory studies are needed. Diaphragm dysfunction is very common and may not correlate with appendicular weakness.

ICUAW is a clinical diagnosis, though many patients may not be able to adequately comply with muscle testing to obtain a diagnostic summated MRC score, substantial inter-observer variation exists in assessing strength with the MRC scale, and the cause of weakness is not elucidated by the definition. Therefore, nerve conduction study (NCS) and EMG can be helpful in excluding other illnesses and confirming electrophysiologic evidence of CINM. CMAPs are typically reduced and prolonged and SNAPs can be diminished in CINM. Abbreviated NCS, such as the peroneal nerve test, was developed with the aim of reducing the time and expense of a full NCS/EMG and has been found to be 100% sensitive, but only 80% specific for the diagnosis of CINM. Direct muscle stimulation has been used to differentiate CIM and CIP (muscle contracts in CIP but not in CIM); however, this may be difficult to perform and interpret in practice. Muscle ultrasound may be a promising aid in the diagnosis of CINM.
There is no specific treatment for ICUAW - aggressive risk factor management is essential to reduce its incidence. Intensive insulin therapy has been shown to reduce the incidence of CINM and the duration of mechanical ventilation, though this practice is not adopted due to a higher associated incidence of hypoglycemic events and overall mortality. Early parenteral nutrition has been associated with an increased incidence of ICUAW and longer recovery relative to late parenteral nutrition. The practice of routine sedation holidays and progressive and early mobilization has been shown to be safe, feasible, and has been associated with a reduction in the duration of mechanical ventilation, the incidence of ICUAW, and an improvement in outcomes. Patients who cannot be mobilized or who are sedated or comatose may benefit functionally and in terms of quality of life from active or passive cycle ergometry and muscle stimulation may reduce disability, though both techniques require further study.

ICU Delirium and Long-term Cognitive Impairment After Critical Illness:

Despite bearing many names, (e.g. encephalopathy, acute brain failure, ICU psychosis), delirium is the preferred nomenclature to describe the spectrum of acute and often fluctuating change in cognition that is characterized by inattention, which occurs in patients as a physiologic consequence of their underlying medical illness or of a medication effect. Billions of healthcare dollars are spent annually as the result of this common condition and resultant complications, which include self-extubation and removal of catheters, prolonged mechanical ventilation and ICU/hospital length of stay, increased mortality, and long-term cognitive impairment.

The development of delirium has been associated with a variety of risk factors including age, dementia, hypertension, pre-ICU emergency surgery or trauma, Acute Physiology and Chronic Health Evaluation (APACHE) II score, mechanical ventilation, metabolic acidosis, delirium on the prior day, multi-organ failure, and coma. A prediction scoring system using many of these risk factors has been validated. Pain, alcohol use, and immobilization have also been implicated. Sleep fragmentation is extremely prevalent amongst ICU patients and may be a risk factor as well. While a recent meta-analysis concluded sedation with benzodiazepines was not associated with a higher incidence of delirium, another recent adjusted analysis found patients receiving continuous infusions of benzodiazepines had a higher incidence of delirium. However, similar to ICUAW/CINM, one of the strongest and most important risk factors for delirium is systemic inflammation and sepsis.

The pathophysiology of delirium is complex and multifactorial, but the most prominent hypothesis relates to systemic inflammation. Inflammatory mediators evoked in this scenario decrease effective oxygen and nutrient delivery into the end organ by impeding capillary flow and increasing diffusion distance through edema. Furthermore, associated disruption of the blood-brain barrier, impaired cerebrovascular autoregulation, and impairment in synaptic transmission has been discovered. Abnormalities in multiple neurotransmitters, including monoamines, acetylcholine, glutamate, and GABA, have also been observed in delirious patients. The association between ICUAW and septic encephalopathy supports the hypothesis of inflammation as a common precipitant for both diseases.

Delirium is a clinical diagnosis – patients can present with a spectrum of severity and patients can be classified into motoric subtypes depending on the clinical manifestations. Patients with hypoactive delirium are characterized by lethargy and psychomotor retardation. While they comprise approximately 45% of delirious patients their symptoms are subler, particularly in the commonly associated context of mechanical intubation and the use of sedation analgesics, and their diagnosis often requires a heightened index of suspicion. Hyperactive delirium, while only accounting for roughly 2% of delirious patients, is easier to recognize as it presents with psychomotor agitation. Mixed delirium encompasses alternating elements of both aforementioned phenotypes and represents the majority of delirious patients.

Several diagnostic tools have been developed to screen for delirium and their employment results in higher rates of detection. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable of such tools. Specifically, the CAM-ICU is designed to detect delirium in nonverbal ventilated patients and yields a dichotomous (i.e. yes/no) result regarding whether the patient is delirious. The ICDSC, conversely, is semi-quantitative with lower scores representing subsyndromal delirium. Both scales have relatively high sensitivity and specificity.
The treatment of delirium involves management of modifiable risk factors and controlling of agitation though pharmacologic and non-pharmacologic methods. Bundled non-pharmacologic interventions, including sleep promotion, noise reduction and earplugs, and early mobilization including occupational therapy have been shown to reduce the incidence and duration of delirium. Multi-component implementation programs integrating comprehensive assessment frameworks (e.g. ABCD bundle or pain, agitation, and delirium management [PAD]) into routine care for risk factor reduction may improve clinical outcome and ICU length of stay. Daily assessment of pain with appropriate treatment has been shown to reduce time on mechanical ventilation and the use of sedatives. Ketamine also has potential as an adjunctive agent for pain control that may be associated with lower rates of delirium. Trials with adjunctive rivastigmine to prevent delirium have shown a trend towards harm. Promising initial results using statins to reduce the incidence of delirium were not confirmed in a recent ancillary study. Haloperidol and risperidone have shown positive results in the post-operative setting to prevent delirium. Additionally, a recent randomized study demonstrated the incidence of perioperative delirium was reduced using dexmedetomidine in patients over 65 years with non-cardiac surgery. Perioperative dexmedetomidine also showed benefit in reducing the incidence of delirium, the incidence of tachyarrhythmias, and ICU and hospital stay in a meta-analysis of patients undergoing cardiac surgery. While results of studies using melatonin have been mixed, the melatonin agonist ramelteon has preliminarily shown to reduce the incidence of delirium in the ICU population. Acute therapy to control agitation is necessary to prevent injury from self-extubation, catheter and line removal, falls, etc. Typical and atypical antipsychotics remain the mainstay of acute treatment of agitation in delirium. Efficacy is similar amongst different agents, but the atypicals may have a lower side effect burden. Uptitrating doses of quetiapine in an algorithmic manner in addition to haloperidol may shorten the duration of delirium. The use of dexmedetomidine in addition to standard care (which includes antipsychotics) for agitated delirium has been associated with a reduction in the duration of mechanical ventilation, the duration of delirium, and ICU length of stay and may be safer and more cost effective than continuing to escalate haloperidol dosing. In practice, the type of drug access available, the patient’s QT interval, the presence of hepatic and renal impairment, and the urgency of agitation treatment may dictate the choice of agent.

Unfortunately, patients who survive delirium and their primary illness are at risk for the development of long-term cognitive impairment. One recent study observed that one-fourth of critically ill patients due to a variety of causes will develop cognitive impairment at one year similar in severity to mild Alzheimer’s disease (though the domain is global as opposed to preferentially involving delayed memory, as seen in Alzheimer’s) and one-third will have cognitive impairment proportional to patients with moderate traumatic brain injury. The duration of delirium correlates with worse cognition independent of age, pre-existing cognitive impairment, burden of coexisting conditions and organ failure, and the use of sedatives/analgesics. Associated structural changes in the brain have also been observed in critically ill delirious patients, and the degree of which is also proportional to the duration of delirium. Specifically, white matter disruption (measured in the corpus callosum and anterior limb of the internal capsule) and brain atrophy (including the frontal lobes, hippocampus, cerebellum, and using ventricle-to-brain ratio) have both been shown to correlate with the degree of cognitive impairment at 12 months. The net effect on the patient overall is increased disability.

Neuropsychiatric Effects of Critical Illness and Post-Intensive Care Syndrome

The incidence of general anxiety, depression, and PTSD in the aftermath of critical illness can range from approximately 10 – 40%, depending on the clinical context and the tools and cutoffs used to evaluate the respective conditions. Depression and anxiety appear to be more common than PTSD, though the conditions very often co-occur. When depression does occur, the symptoms appear to be more driven by somatic as opposed to cognitive components, which tend to be more resistant to antidepressants and may benefit more from rehabilitation. Risk factors for the occurrence of PTSD after critical illness include benzodiazepine administration, memories of frightening experiences in the ICU (which may be related to hallucinations seen while delirious), and comorbid psychopathology. The use of an ICU diary is associated with a reduction in PTSD symptoms. The presence of post-ICU psychological illness is associated with reduced functional status and quality of life.

Post-intensive Care Syndrome is a term that encompasses the entire spectrum of physical, cognitive, and psychological issues patients and their families face in the aftermath of critical illness. Checklists aimed at identifying and mediating the similar risk factors for the aforementioned conditions in addition to family education, psychological support, and follow-up may improve outcome and quality of life for critically ill patients.
References:
