Acquired Brain Injury in the Pediatric Intensive Care Unit: Special Considerations for Delirium Protocols

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Abstract

Keywords

- critical care
- pediatrics
- delirium
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- agitation

The goal of this article was to highlight the overlapping nature of symptoms of delirium and acquired brain injury (ABI) in children and similarities and differences in treatment, with a focus on literature supporting an adverse effect of antipsychotic medications on recovery from brain injury. An interdisciplinary approach to education regarding overlap between symptoms of delirium and ABI is important for pediatric intensive care settings, particularly at this time when standardized procedures for delirium screening and management are being increasingly employed. Development of treatment protocols specific to children with ABI that combine both nonpharmacologic and pharmacologic strategies will reduce the risk of reliance on treatment strategies that are less preferred and optimize care for this population.

Overview of PICU Delirium

The last decade brought forth increased efforts to optimize the care of children in the pediatric intensive care unit (PICU) through improved identification, prevention, and treatment of delirium.^{1–4} In adults, delirium is defined as a disturbance in attention or awareness accompanied by change in cognition.⁵ Delirium develops over a short period of time, fluctuates in course, and is a consequence of underlying medical conditions, iatrogenic exposures, and environmental factors during peri-

ods of critical illness. The concept of pediatric delirium has been adopted from this adult definition, as neither Diagnostic and Statistical Manual of Mental Disorders, fifth edition nor International Classification of Diseases, 10th revision includes a definition of delirium specific to pediatrics.² The delirium classification used in adults of hyperactive, hypoactive, and mixed subtypes has also been applied in children.⁶ Literature regarding delirium in the pediatric population is growing but currently remains limited. The prevalence of pediatric delirium in surgical, medical, and cardiac ICUs is reported to range

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from 12 to 65%.⁷ In the largest multicenter study that included an assessment of 994 pediatric patients, overall prevalence was 25%⁸ with hypoactive (46%) and mixed (45%) subtypes being most common.⁴

Risk factors for pediatric delirium are similar to those identified in adults.^{4,9} These include (1) predisposing factors, that is, extremes of age (< 2 years), severity of illness, developmental delay and (2) precipitating factors such as use of mechanical ventilation, history of coma, and use of benzodiazepines or anticholinergics. Delirium in critically ill children is associated with increased mortality, duration of mechanical ventilation, hospital length of stay, and hospital cost.⁴

The exact pathogenesis of delirium is currently not fully understood at this time in adults, with even less information in the pediatric population. Derangements in the acetylcholine and dopaminergic neurotransmitter systems¹⁰ have been implicated as well as inflammatory mediators¹¹ that are present in sepsis and shock. Oxidative stress¹¹ due to decreased oxygen delivery to the brain has also been suggested, being most noticeable in patients undergoing cardiac surgery.¹² Management strategies for delirium include low-risk, nonpharmacological interventions, and in some cases, antipsychotic medications.¹³

Acquired Brain Injury and Delirium

While addressing delirium is an important strategy in optimizing ICU care, the child with acquired brain injury (ABI) requires special consideration. ABI is classified based on etiology as either (1) traumatic brain injury (TBI), an alteration of the brain caused by an external force, or (2) nontraumatic brain injury (ntBI), representing injuries caused by internal stimuli such as stroke, infection, hypoxemia, seizures, metabolic derangement, or tumor.

ABI presents with symptoms overlapping those of delirium (→ Table 1), such that a child with ABI will often screen positive for delirium. While ABI and delirium may coexist, pharmacologic management of delirium may present unique risks to patients with ABI, such that there may be harm to including children with ABI receiving standard delirium screening and treatment.

Pediatric ABI is a common reason for PICU admission. Pediatric TBI resulted in 288,000 hospitalizations across the

United States in 2014.¹⁴ ntBI (excluding stroke) accounted for 82.3 hospitalizations for 100,000 children in a study of Ontario hospitals, with 35% requiring PICU settings.¹⁵ Ischemic stroke affects an estimated 1.0 to 2.0 in 100,000 children (nonneonates) annually in Western developed countries, whereas hemorrhagic stroke accounts for about half of pediatric stroke, with an incidence of ≈1 to 1.7 in 100,000 per year.¹⁶

ABI frequently results in variable alterations of cognitive-behavioral functioning that can contribute to challenges in identifying manifestations of delirium versus ABI (→ Table 1). In the most severe forms of ABI, a child may meet criteria for a disorder of consciousness (coma, vegetative state, or minimally conscious state), indicating that the child does not demonstrate typical levels of awareness and responsiveness to the environment.^{17,18} While some patients with ABI demonstrate significant behavioral dysregulation presenting as agitation, irritability, or impulsivity, in other cases, memory and attention may be impacted without agitation. After TBI, there is commonly a period of posttraumatic amnesia (PTA)¹⁹ in which a child has difficulty laying down new memories. Thus, the child may be confused and require frequent reorientation, despite demonstrating intact memory for well-learned preinjury historical information. Symptoms of delirium may overlap with other conditions, such as hypnotic-related iatrogenic withdrawal syndrome²⁰ or the anticholinergic syndrome.²¹ However, distinguishing children with ABI versus delirium is critical because of the difference in management approaches for the two conditions, most notably with regard to pharmacologic interventions and specifically the use of antipsychotic medications.

This overlapping presentation makes it challenging to identify the true frequency of delirium in patients with ABI. Patel et al conducted a systematic review of seven prospective cohort studies which utilized various delirium screening tools in 1,173 neurocritically ill adult patients with ABI. The reported pooled prevalence rate of positive screening for delirium was 12 to 43%, with variability in patient populations and severity of ABI likely contributing to the range in findings. The screening tools used were the Confusion Assessment Method for the ICU, the Intensive Care Delirium Screening Checklist, the 4-A test, and the Confusion Assessment Method.²² The authors highlighted the challenge in interpreting these data given that, in the neurocritically ill population, a

Table 1 Common symptoms of delirium and acquired brain injury in children

Symptoms more specific to delirium		Symptoms overlapping between delirium and acquired brain injury	Symptoms more specific to acquired brain injury
Hyperactive	• Psychosis	• Agitation • Inattention/impulsivity • Irritability, crying • Decreased sleep • Motor restlessness	• Focal neurologic signs • Receptive and/or expressive aphasia • Dysarthria • Motor impairment • Sensitivity to light and/or noise
Hypoactive		• Somnolence/increased sleep • Decreased responsiveness • Decreased verbal/play interactions • Loss of developmental milestones	

positive delirium screen may reflect the underlying neurological disease or its sequelae, and emphasized the importance of individually evaluating each patient to appropriately direct treatment.

Diagnostic Considerations

Given the wide variation in ABI presentation, symptoms of delirium and brain injury are generally nonspecific and overlapping, which can lead to children with ABI screening positive when delirium screening tools are used in the PICU setting. For example, the Cornell Assessment of Pediatric Delirium (CAPD)²³ was developed as a nursing screening tool by Traube et al. Symptoms and signs queried by the CAPD include decreased awareness/eye contact, decreased purposeful movements, difficulty communicating needs, increased restlessness, decreased consolability, diminished activity when awake, and increased response time to interactions with the environment, all of which may be present in delirium and/or ABI.

While sensitivity of the CAPD is high, specificity is poor in children with functional impairments. The overall false-positive rate of the CAPD in a pediatric population was 17%; most of these false positives being in patients with baseline developmental delays.²³ In patients with developmental delay, the CAPD had 96.2% sensitivity and 51.2% specificity rates.²³ To address the decreased specificity in patients with developmental delay, using the CAPD in combination with the Richmond Agitation and Sedation Scale to differentiate fluctuating versus static deficit has been suggested.²⁴ While some patients with ABI were included in the initial validation of the tool, the CAPD has not been specifically validated for ABI patients as a subgroup or modifications suggested.²³

While our group has experience with the CAPD as our institutional delirium screening tool, there are several other delirium screening tools for pediatric ICUs. The Pediatric Confusion Assessment Method for the ICU for children 5 years of age and older and PreSchool Confusion Assessment Method for the ICU for patients between 6 months and 5 years of age has been adapted from the adult CAM ICU.²⁵ Of note, the CAM-ICU has been specifically considered with regard to use in adults with TBI, and caution has been suggested given the problem of overlapping symptoms yielding decreased sensitivity and specificity for delirium in adults with TBI compared with those without TBI.²⁶ Other validated pediatric delirium tools include Pediatric Anesthesia Emergence Delirium Scale (PAEDS)²⁷ which was the precursor of the CAPD and the more recently described Sophia Observation Withdrawal Symptoms–Pediatric Delirium (SOS-PD) scale.²⁸ The validity of the PAEDS and SOS-PD in the brain injury population has not been evaluated.

Treatment Considerations

There are several special considerations when determining management of symptoms consistent with delirium versus ABI in the hospital setting. For all children, a positive screen for delirium should trigger a more exhaustive evaluation to determine underlying reversible causes.²⁰

In both patients with delirium and/or ABI, first-line measures include minimizing sedative exposure, promoting natural sleep-wake cycles including natural light exposure, controlling the level of stimulation, and encouraging early mobilization.

As a second line of symptom management for hyperactive delirium, atypical antipsychotic medications have been proposed for agitation.²⁹ However, the use of atypical antipsychotic requires caution in pediatric patients for several reasons.^{1,30} First, data regarding safety and effectiveness of atypical antipsychotic use in critically ill children are limited.²⁹ Second, in some settings, prolonged postdischarge use of ICU-initiated antipsychotics may occur due to a lack of a weaning plan or specialist follow-up.^{31,32} Continued use of antipsychotics can be associated with adverse effects such as a prolonged QT syndrome, neuroleptic malignant syndrome, and extrapyramidal symptoms, weight gain, increased risk of diabetes, and sedation.³¹

For children with ABI, limited literature from animal and adult TBI studies suggests that antipsychotic medications pose even greater risks. Studies in both adults³³ and children³⁴ demonstrate an adverse effect of antipsychotics on recovery such that the use of antipsychotic medications is consistently discouraged in early treatment of ABI. In adults with TBI and agitation, patients treated with haloperidol experienced a longer period of PTA.³⁵ In a rat model of TBI, both haloperidol and risperidone were shown to impair spatial learning, and risperidone was also associated with delayed motor recovery.³⁶ These adverse effects on recovery are thought to be due to interference with the adrenergic, dopaminergic, and cholinergic pathways that are essential in neuronal recovery.³⁶

While some benefits have been observed with the use of newer antipsychotics in individuals with ABI in critical care settings, there has not been rigorous enough study to assume these medications do not interfere with longer term recovery in light of the findings discussed earlier. Ziprasidone was reported to be effective in managing agitation in children with TBI in the PICU setting, though this came at a cost of significant sedation.³⁷ In one cohort of adults with TBI, quetiapine is reported to have short-term benefit in the acute ICU period, possibly through impacts on improving intracranial pressure and cerebral perfusion pressure. Longer term effects on recovery remain unknown and caution would still be suggested as quetiapine interferes with dopaminergic pathways.³⁸

As in treatment for delirium, environmental measures are the first line for optimizing cognitive/behavioral functioning after ABI. Agitation is frequently found after ABI and is often associated with difficulty processing information, confusion, and disorientation. In this setting, the use of sedating medications such as benzodiazepines and anticholinergic medications should be avoided due to their potential to compound confusion and to further worsen agitation.^{39,40}

Due to these established concerns regarding the effect of antipsychotic and benzodiazepine medications on recovery from ABI, alternate pharmacologic interventions are recommended for symptom management in patients with ABI. Gabapentin is utilized for neuropathic-related pain as well as

neuroirritability⁴¹ and paroxysmal sympathetic hyperactivity (PSH) symptom management.⁴² In adults, propranolol is well studied as a treatment for agitation and it is also commonly used in children with ABI to treat both PSH and agitation.^{18,43,44} Sympathetic hyperactivity has also been implicated in postbrain injury agitation, such that decreasing hyperadrenergic activity with propranolol^{33,45} or inhibiting the release of norepinephrine at the presynaptic α -2 receptors with clonidine or dexmedetomidine may be beneficial.^{43,45,46} Recently, decreased in-hospital mortality and improved functional outcomes at 6 months was reported with the early use of propranolol in adults with TBI, thought to be related to its effects of reducing hyperadrenergic activity and improving cerebral circulation.⁴⁷ Both clonidine and propranolol are also used for neuroirritability. Melatonin and trazodone are preferred for addressing difficulty with sleep onset and maintenance, respectively. Amantadine is a dopaminergic agonist that has improved rates of recovery in adults with disorders of consciousness after TBI, as well as irritability and abnormal behavior.¹⁸

Suggested Approaches for Delirium Screening in ABI Patients

Further research to determine the effectiveness of delirium screening in brain injury should be considered. In the meantime, in light of the poor specificity of delirium screening tools in children with ABI and the potential risk of harm with use of antipsychotic medications, children with ABI merit special consideration when designing and implementing delirium screening procedures.

In our experience, successful strategies to decrease the likelihood of misdiagnosing delirium in a child with ABI include:

- Interprofessional collaboration (ideally including intensive care, neurology, neurosurgery, psychiatry, rehabilitation medicine, rehabilitation therapists, and nursing) to optimize evaluation and management of children with delirium and/or ABI.
- Education efforts to increasing provider awareness of the overlap in symptoms between delirium and ABI.
- Consider a collaborative delirium screening model led by physicians for patients with brain injury.
- A specific screening tool is not recommended; however, we do suggest that regardless of the tool used, there needs to be special considerations for patients with ABI.
- Development of specific protocols for patients with ABI and agitation to decrease the use of pharmacologic management strategies utilized for patients with delirium without ABI. In our experience, this may be achieved through collaboration among the interdisciplinary team to evaluate evidence and recommendations for agitation management based on literature reviews^{43,48,49} and determine site-specific recommendations for use of medications in light of the patient population and provider preferences.

Conclusion

Symptoms of delirium and ABI can frequently overlap in the PICU setting. Without special procedures/considerations for

children with ABI, pathway-driven treatment for delirium can lead to the overuse of antipsychotic drugs reported to interfere with neurologic recovery in ABI patients. An interdisciplinary approach to education and development of treatment protocols that combine both nonpharmacologic and adequate pharmacologic strategies will be paramount in providing optimal care for our patients.

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Conflict of Interest

None declared.

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