Delirium in Pediatric Critical Care

Anita K. Patel, MD[a], Michael J. Bell, MD[b,c,d], Chani Traube, MD[e,*]

KEYWORDS

• Delirium • Pediatric critical care • Pediatrics • Pain • Agitation • Sedation

KEY POINTS

- Delirium is a frequent and serious complication of pediatric critical illness.
- Pediatric delirium is associated with increased morbidity, including longer duration of mechanical ventilation, increased hospital length of stay, and higher resource utilization.
- Benzodiazepines likely increase the risk for development of pediatric delirium.
- Delirium in children is both treatable and preventable.

DELIRIUM IN PEDIATRIC CRITICAL ILLNESS

Introduction

As critical care medicine has matured over the decades, from a specialty fighting mortality from a myriad of diseases to one promoting recovery with as few disabilities as possible, mitigating complications of critical illness has become one of the intensivist's most important goals.[1] The sudden onset of unexplained deterioration of consciousness can be particularly worrisome. In critical illnesses such a deterioration of sensorium may represent delirium, which is characterized by an acute onset and fluctuating course with disturbances in awareness and cognition.[2] In adults, delirium occurs frequently and represents global cerebral dysfunction due to the direct physiologic effects of an underlying medical illness or its treatment.[2,3] Although delirium is generally a temporary state, it is strongly associated with poor outcomes, including increased mortality, and long-term cognitive impairment in survivors.[4,5] Because of the extensive research highlighting the morbidity associated with delirium, the Society of Critical Care Medicine (SCCM) released guidelines in 2013 that recommended routine

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[a] Pediatrics, Children's National Medical Center, 111 Michigan Avenue Northwest Suite M4800, Washington, DC 20010, USA; [b] Critical Care Medicine, University of Pittsburgh, 3434 Fifth Avenue, Pittsburgh, PA 15260, USA; [c] Neurological Surgery, University of Pittsburgh, 3434 Fifth Avenue, Pittsburgh, PA 15260, USA; [d] Pediatrics, University of Pittsburgh, 3434 Fifth Avenue, Pittsburgh, PA 15260, USA; [e] Pediatrics, Weill Cornell Medical College, 525 East 68th Street, M-508, New York, NY 10065, USA
* Corresponding author.
E-mail address: chr9008@med.cornell.edu

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monitoring for delirium in critically ill adults as standard of care.[3] A recent body of pediatric literature suggests that this recommendation should apply to children as well.[6,7]

Pathophysiology

The cause of delirium is complex, with many possible pathophysiologic pathways. Most researchers think that delirium results from a combination of predisposing and precipitating factors. Predisposing factors are patient related (for example, age, genetic susceptibility, or underlying disease). Precipitating factors include treatment effects (particularly sedative medications) and the intensive care unit (ICU) environment.[3,8,9] Here the authors highlight 3 processes that are thought to play important roles in the evolution of pediatric delirium.

The *neuroinflammatory* hypothesis suggests that systemic inflammation (commonly seen during critical illnesses, such as respiratory failure, sepsis, and others) leads to either compromise in the integrity of the blood-brain barrier or de novo production of inflammatory products within the brain.[10] Inflammation leads to endothelial activation, enhanced cytokine activity, and infiltration of leukocytes and cytokines into the central nervous system (CNS), producing local ischemia and neuronal apoptosis.[11] Several studies have demonstrated elevated levels of proinflammatory cytokines in delirious patients (such as C-reactive protein, tumor necrosis factor-alpha, and interleukin-6) compared with nondelirious patients, even after controlling for age and cognitive impairment.[12–14]

The *neurotransmitter* hypothesis was generated from clinical observations that delirium often followed the use of medications that change neurotransmitter function.[10] Studies show that impaired cholinergic function, coupled with an excess of dopaminergic transmission, leads to the development of delirium.[15–17] Notably, anticholinergic medications are tightly associated with development of delirium in the geriatric population, as the elderly have an age-related reduction in acetylcholine synthesis.[18,19] (Intriguingly, a similar phenomenon may exist in children less than 2 years of age, whereby functional MRIs have demonstrated sparse connectivity between control structures related to executive function. This sparse connectivity results in dependence on the cholinergic system to modulate attention and orientation. Like the elderly, these young children may be at particular risk of delirium with exposure to anticholinergic medication.)[20,21] In addition to dopamine and acetylcholine, dysregulation of melatonin, glutamate, norepinephrine, serotonin, histamine, and gamma-aminobutyric acid has also been suggested to contribute to delirium development.[10]

The *oxidative stress* hypothesis suggests that reduced oxygen delivery in critical illness, coupled with increased cerebral metabolism, leads to the production of reactive oxygen species that cause global CNS dysfunction.[10] Hypoxia has clearly been associated with delirium development.[22–24] For instance, a study of patients undergoing cardiac surgery found that intraoperative desaturation was an independent risk factor for postoperative delirium.[23] Demonstrating that overlapping sources of pathophysiology contribute to delirium, hypoxia also results in an excess of dopamine due to the failure of the oxygen-dependent conversion of dopamine to norepinephrine. The enzyme responsible for dopamine degradation, catechol-o-methyl transferase, is inhibited by toxic metabolites produced during oxidative stress.[22] An excess of dopamine has been evidenced in multiple studies to underlie the pathogenesis of hyperactive delirium.[10]

Regardless of the exact pathophysiology that triggers an episode of delirium, the end result is the same: altered neurotransmission that leads to a failure of integration and processing of sensory information and motor response. This final common pathway leads to the behaviors that we recognize as delirium.[25]