INTRODUCTION

Delirium is a common and serious sequel of critical illness. Children with neuroblastoma may be at particular risk during the post-operative period. Unfortunately, most pediatric oncologists, surgeons, and intensivists are not aware of this issue, and do not routinely screen children for the development of delirium. In our pediatric intensive care unit, we admit approximately 35 children with stage 4 neuroblastoma each year for post-operative management after extensive thoracoabdominal resection. In this case series, we highlight some typical patients who were diagnosed with delirium, discuss risk factors, and suggest a treatment plan (Table I). The institutional review board reviewed this report and waived the need for approval.

Delirium is defined as an acute and fluctuating change in mental status, associated with disordered cognition and attention, due to an underlying medical condition or treatment thereof [1]. There are three subtypes of delirium: hyperactive, hypoactive, and mixed. In adults, delirium is associated with increased mortality, increased length of hospitalization, and post-discharge cognitive impairment [2]. An emerging pediatric literature suggests a prevalence of 15–20% in critically ill children with associated long-term morbidity [3–6].

Pediatric delirium is complicated by developmental variability—normal behavior in a 2-year-old is clearly abnormal in a 12-year-old—but with attention to developmental expectations, it can be diagnosed as reliably as in adults [3,4,7]. Delirium in children is notable for changes in psychomotor activity (restlessness in hyperactive delirium, and underactivity in hypoactive delirium). In extremely young or mechanically ventilated children, delirium may present as refractory agitation [8–10].

Neuroblastoma is the third most common pediatric cancer, and accounts for 15% of all pediatric cancer deaths. More than 600 cases are diagnosed in the US annually, with median age at presentation of 17 months. A tumor of the sympathetic nervous system, it is composed of primitive sympathetic ganglion cells. Multi-modality treatment consists of chemotherapy, radiation, surgical resection, and stem cell transplantation [11–12].

Children with neuroblastoma possess many underlying risk factors thought to predispose patients to delirium. These include high severity of illness at admission, underlying malignancy, sympathetic overdrive, mechanical ventilation in post-operative period, and need for opiates and sedatives [2,6,13].

In our pediatric intensive care unit, we screen for delirium twice daily using the Cornell Assessment of Pediatric Delirium, an 8-item rapid bedside observational tool completed by the nurse [4]. Positive screens are flagged for evaluation by the pediatric intensivist or child psychiatrist who use the gold-standard criteria of the Diagnostic and Statistical Manual of Mental Disorders to diagnose delirium [1].

Children diagnosed with delirium are then treated in four ways: (1) Treat the underlying disease processes predisposing to delirium (i.e., sepsis with inflammatory cascade, or fever). (2) Address iatrogenic factors, particularly those that are medication-related. Minimize anticholinergics and benzodiazepines, titrate opiates to treat pain (not agitation), and consider dexmedetomidine (an alpha-2 agonist with anxiolytic effect) for sedation. (3) Mitigate the environmental triggers: minimize sleep interruptions, facilitate early mobilization, exposure to natural light when possible, use of eyeglasses when appropriate, and introduction of familiar and comforting objects (i.e., favorite blanket or music). (4) When modification of medications and environmental factors are insufficient, employ pharmacologic intervention, specifically quetiapine, an atypical antipsychotic with a favorable risk profile [14,15] (as compared to typical antipsychotics such as haloperidol).

With early detection and treatment, the duration of delirium can be shortened, thereby facilitating weaning from mechanical ventilation and post-operative recovery.

CASE EXAMPLES

Case 1

A 3-year-old male with Soto syndrome and stage IV neuroblastoma was admitted to the PICU for post-operative care following thoracoabdominal resection, including right adrenalectomy, lymph node dissection, and liver biopsy. At baseline, the patient was nonverbal with significant developmental delay. Post-
operative course was notable for extreme agitation, treated with high dose midazolam (approximately 0.2 mg/kg/hour) and fentanyl (approximately 4 mcg/kg/hour) infusions to prevent self-extubation. When sedation was decreased, patient-ventilator dysynchrony was noted. The patient had sporadic restless movements of the arms and legs, minimal eye contact, and no appreciable sleep/wake cycle. His mother described him as “possessed” and claimed that he did not seem to recognize her. On the fifth post-operative day, he was diagnosed with delirium. Anticholinergic medications and benzodiazepines were discontinued, and he was started on quetiapine. He improved within 24 hours and was successfully extubated the following day.

**Case 2**

A 27-month-old female with cervical neuroblastoma encasing the aorta and vagus, hypoglossal, and recurrent laryngeal nerves was admitted for post-operative care after resection. PICU course was complicated by vocal cord paresis and prolonged intubation. On sixth post-operative day, she was noted to have worsening agitation, with ventilator dysynchrony, thrashing in bed, no eye contact or purposeful activity, and no sustained sleep. She was diagnosed with delirium, weaned from benzodiazepines, and started on quetiapine. Within 24 hours agitation subsided, and she had improved eye contact and communication. This facilitated weaning of opiates and sedatives and successful extubation.

**Case 3**

A 3-year-old female with stage IV neuroblastoma was admitted for post-operative care following extensive thoracoabdominal resection complicated by acute renal failure. In the immediate post-operative period, she required extensive volume resuscitation, vasopressors for hypotension, and stress dose steroids for adrenal insufficiency. When shock resolved, sedation was lightened and she was noted to have a fluctuating mental status, sometimes extremely agitated and combative, and other times withdrawn, with delayed motor response to interactions. Her mother described her as “in a trance”. Delirium was diagnosed and targeted interventions ensued, including replacing benzodiazepines with dexmedetomidine for sedation, minimizing opiates, avoiding anticholinergics, optimizing continuous veno-venous hemofiltration (CVVH) to normalize blood urea nitrogen, and clustering care to avoid nighttime awakenings. Agitation improved but she remained withdrawn and confused. With initiation of quetiapine, confusion improved. Quetiapine was continued for approximately 10 days, and tapered off prior to discharge home.

**CONCLUSION**

Delirium is the most frequently diagnosed neuropsychiatric complication of advanced cancer in adults, and an independent risk factor in predicting short-term survival [16–17]. The prevalence of delirium in pediatric oncology patients is not well-described, largely due to the absence of widespread screening. Pediatric oncologists are at the front lines with respect to detecting delirium in their high-risk patient population. Widespread screening is feasible, even in extremely young and mechanically ventilated patients. Targeted treatment may shorten the duration of delirium and mitigate associated morbidities. Heightened awareness by pediatric oncologists, surgeons, and

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<td>Care clustered</td>
<td>BUN and electrolytes normalized</td>
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intensivists may lead to earlier diagnosis and improvement in clinical outcomes. Children with neuroblastoma have underlying factors that may constitute an increased risk for delirium, especially in the post-operative period. A prospective multi-institutional trial to investigate the prevalence of delirium in neuroblastoma patients, and identify modifiable risk factors, is warranted.

REFERENCES