Diagnosis and Management of Delirium in Critically Ill Infants: Case Report and Review
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Delirium is a disturbance in attention and awareness that develops as a change from baseline over a short period of time (hours to days) and tends to fluctuate in severity during the course of the day. It has an added component of disturbance in cognition that is not explained by another neurocognitive disorder and there is evidence that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal, exposure to toxin or multiple etiologies.1 Adult delirium is increasingly recognized using scales to screen for symptoms and treated with evidence-based milieu interventions, elimination of iatrogenic causes, and antipsychotic medications.2 How this applies to children has been a subject of much interest and research.3–6 The available evidence in children is largely based on case reports/series and retrospective studies with a lack of prospective trials to assess efficacy of interventions, including medications. Patients in

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ICUs are vulnerable to delirium, and it results in morbidity and mortality in addition to that arising from underlying medical processes, making it important to diagnose and treat early.1,2 Some studies indicate that mortality in children from delirium is comparable to that in adults.3–11 A large percentage of children admitted to PICUs are infants.12–14 They often have congenital abnormalities, multiple medications, or laboratory changes with resultant risk for corrected QT interval (QTc) prolongation. Attempts at understanding pediatric delirium must include infants and a careful weighing of risks from untreated delirium versus potential antipsychotic induced QTc worsening and arrhythmias.4 The current literature in infant delirium is limited and evolving, with few guidelines for those with cardiac risks. This presents a significant challenge in addressing the question of considering off-label medication management in this group when other measures fail. Here we present a case of infant delirium in the setting of several risk factors in which the infant responded to medication without worsening of QTc interval.

Case

Infant K was born with a complete atrioventricular septal defect, aortic arch hypoplasia, and left ventricular hypoplasia with trisomy 21.3 In the first 5 months of life, she had a Norwood repair with delayed chest closing and angioplasty for coarctation of the aorta. At 5.5 months, she was hospitalized for a bidirectional Glenn shunt procedure and developed sepsis with hypoxemia requiring ventilator support. Two months into this hospitalization, she exhibited agitation with motor restlessness at rest and in response to sounds and touch, new-onset sleep-wake cycle disruption, and vital sign destabilization. Her mother reported this as an abrupt change, and Infant K was inconsolable during these episodes. Attempts to manage the agitation with high-dose morphine and lorazepam were unsuccessful (Table 1), leading to a pediatric psychiatry consult to assist in assessment and further management of agitation.

Initial psychiatric assessment revealed multiple medical problems as noted earlier and multiple medications (Table 1). A cross taper from high-dose morphine to methadone and escalating use of lorazepam for agitation were of particular temporal significance (Table 1). The onset of symptoms was sudden, fluctuated throughout the day, and led to changes in heart rate (110–143 beats per minute), respiratory rate (20–36 breaths per minute), and blood pressure (77–121/22–63 mm Hg); her weight was 7.8 kg. Laboratory results at evaluation are summarized in Table 2. Juxtaposing her presentation with case reports of infant delirium presenting with motor restlessness and agitation,15 a provisional diagnosis of delirium due to multiple etiologies was made.

We recommended environmental measures to reduce sleep disruption and increase presence of familiar objects/people.16 We also suggested they taper benzodiazepines, stabilize opiates by eliminating fluctuating morphine dosing with a switch to methadone while monitoring QTc and avoid antihistaminergic/anticholinergic medications as much
TABLE 2 Laboratory Values

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>148 mEq/L</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>16 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14.6 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>45.8%</td>
</tr>
<tr>
<td>Total protein</td>
<td>5.2 g/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.8 g/dL</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.3 mg/dL</td>
</tr>
<tr>
<td>Aspartate transaminase</td>
<td>37 U/L</td>
</tr>
<tr>
<td>Bilirubin direct</td>
<td>0.5 mg/dL</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
</tr>
<tr>
<td>D-dimer</td>
<td>8950 mcg/L</td>
</tr>
<tr>
<td>TSH</td>
<td>1.89 μIU/mL</td>
</tr>
<tr>
<td>Free T4</td>
<td>1.33 ng/dL</td>
</tr>
<tr>
<td>Ammonia</td>
<td>36 μg/dL</td>
</tr>
<tr>
<td>EKG</td>
<td>Normal sinus rhythm</td>
</tr>
<tr>
<td>QTc</td>
<td>475 ms</td>
</tr>
</tbody>
</table>

CBC, complete blood count; TSH, thyroid-stimulating hormone.

as possible.5,16 Some medications potentially contributing to her delirium and QTc prolongation17,18 were continued because of medical necessity (Table 1). Over the next 2 weeks, attempts to improve sleep-wake patterns, reduce lorazepam use, and switch to methadone were made (Table 1). Antipsychotics were not started immediately given the limited information for treatment of infant delirium, her prolonged QTc interval (475 msec), methadone’s tendency to prolong QTc, concern for worsening QTc and arrhythmias from adding antipsychotics, and the off-label nature of its use in infants. Her symptoms persisted despite these changes, and given the risk of vital sign instability leading to further morbidity and mortality, a cautious trial of low-dose atypical antipsychotic (risperidone 0.125 mg at bedtime via nasogastric tube) with close monitoring of QTc interval was recommended. Infant K’s motor restlessness subsided after three doses of risperidone. She tolerated this without QTc prolongation beyond baseline. In the following weeks, she experienced pulmonary edema with reemergence of delirium, and the risperidone was gradually increased to 0.3 mg at bedtime with benefit and without QTc prolongation or other side effects. As her delirium resolved, the risperidone was tapered off over 6 weeks.

Discussion

Delirium in children is common7 and increasingly diagnosed in the PICU setting.4 Those with neurologic, infectious, or respiratory issues are at higher risk.16 It is important to remember that some patients experience the agitation or hyperactive delirium, whereas others present with hypoactive symptoms.19 Like adults,2 children potentially experience morbidity and mortality related to delirium and may experience symptoms of posttraumatic stress, even without conscious memory of the episode.20 Nearly 75% of PICU patients are younger than 3 years, and almost half of those are under 1 year, making it imperative to further our understanding of infant delirium.12–14 Due to inherent communication limitations in infants, accurate diagnosis relies on symptom observation rather than patient interview. Understanding infant orientation and cognition and how delirium disrupts these will help us diagnose and treat in a developmentally salient fashion. Published case reports/series describe a pattern of significant motor restlessness, agitation and difficulty with being soothed as indicative of infant delirium of the hyperactive subtype.16,21,22 Scales such as the Pediatric Confusion Assessment Method for the ICU have been validated for use in children 5 years of age or older,5 and Delirium Rating Scale can be used in younger children, with the exception of items needing advanced orientation skills and assessment of hallucinations.5 The Cornell Assessment of Pediatric Delirium is a developmentally sensitive observational tool for use in a broader age range.3

Once diagnosed, treatment of infant delirium remains a challenge. General principles of treatment should include environmental interventions (access to natural light during the day and darkness at night, frequent orientation, presence of familiar objects/people, sleep hygiene), limiting events/medications that may worsen delirium21 implemented in parallel to treatment of underlying causes of delirium. Opiates and benzodiazepines frequently worsen delirium and are often used for sedation in the ICU setting. There is increasing evidence for the use of dexmedetomidine as an alternate sedating agent with decreased rates of delirium,4,22 although there may be dose/indication-based restrictions on its use in the PICU.24 When these interventions do not lead to symptom resolution, antipsychotics are the mainstay of delirium psychopharmacology, although they are off-label for such use in children.5 They are shown to be effective in adults and children in case reports and retrospective studies. Both typical and atypical antipsychotics are used, with predominately atypical antipsychotic use in children.16,23,25–28 There is limited data for their use in infant whom congenital abnormalities, laboratory abnormalities, or multiple medications compound the risk for antipsychotic-induced QTc prolongation. Treating infants with these cardiac risk factors is challenging given the potential for arrhythmias with lethal consequences. This needs to be carefully balanced against the risk from untreated delirium because patients may remove lines and tubes when agitated, leading to increased morbidity and mortality.12 Besides a case report on infant delirium after cardiac surgery,29 there is limited information to guide treatment in these vulnerable infants.
Although most PICU patients receive continuous cardiac monitoring, additional monitoring of QTc, electrolyte levels, and drug interactions during the introduction and course of antipsychotic treatment is necessary. Antipsychotic treatment cessation must be considered with significant QTc prolongation from baseline. Increase of >30 milliseconds should raise concerns, more so when increased >60 milliseconds, especially when QTc prolongs beyond 500 milliseconds, new T-wave abnormalities emerge, and marked bradycardia or a Brugada phenotype occurs.30 Congenital long QT syndrome studies and case reports show that QTc >500 milliseconds causes a substantially increased risk of cardiac events.26 All atypical antipsychotics should be avoided in children at high risk when QTc >60 milliseconds, best if QTc prolongs beyond 500 milliseconds, new T-wave abnormalities emerge, and marked bradycardia or a Brugada phenotype occurs.30 Congenital long QT syndrome studies and case reports show that QTc >500 milliseconds causes a substantially increased risk of cardiac events.26 All atypical antipsychotics should be avoided in children at high risk when possible.26

Intravenous haloperidol is particularly known to cause a substantially increased risk of cardiac events.26 All atypical antipsychotics show similar cardiac risks and need for monitoring in adult studies. Several studies,33–35 including a systematic review and meta-analysis of the effects of 9 antipsychotics on QTc prolongation in children and adolescents, found no difference compared with placebo.34 However, each instance should be evaluated individually to balance the unique risks for arrhythmia against that from untreated delirium, such as respiratory compromise and brain anoxia.

Conclusions

Delirium is associated with increased morbidity and mortality. Infant delirium may present as a hyperactive subtype with intermittent motor agitation and inconstabubility. Given the negative consequences of untreated delirium, its timely diagnosis and treatment is important. Treatment often includes addressing the underlying causes, environmental alterations, and, if needed, antipsychotics. There is a need for further investigation of the safety and tolerability of these psychopharmacological agents in infants, especially those with other risks for prolonged QTc with prospective studies. Finally, although there is reason to consider treatment when benefits outweigh the risks, this should always be done cautiously and with close monitoring.

ABBREVIATION

QTc: corrected QT interval

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