Pediatric COVID-19 Delirium: Case Report of 2 Adolescents

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ABSTRACT

Introduction: Neurological complications of COVID-19, including delirium, are emerging in the adult population but have not been well described in pediatrics.

Case Presentation: We report the cases of 2 adolescent males, ages 16 and 17, who presented with delirium secondary to an acute COVID-19 infection in the fall of 2020 at Children's Wisconsin in Milwaukee, Wisconsin. The foundation of our treatment strategy was the triad of alpha-2 agonists (clonidine, dexmedetomidine, guanfacine), antipsychotic agents (quetiapine, haloperidol, olanzapine), and melatonin. Discharge planning required involvement from inpatient psychiatry, case management, social work, and the family. Both patients showed improvement after several weeks.

Discussion: We believe these are the first reported cases of COVID-19-associated delirium in children outside of multisystem inflammatory syndrome in children (MIS-C).

Conclusion: Pediatric COVID-19 delirium is a new manifestation of the COVID-19 disease. Treatment guidelines are emerging and lessons regarding therapies and discharge considerations are described in these 2 unique cases.

INTRODUCTION

A growing body of literature describes COVID-19 neurological complications in adults, ranging from headache and dizziness to encephalopathy and delirium.[1-7] SARS-CoV-2, the virus that causes COVID-19, may infect neural cells via angiotensin-converting enzyme 2 (ACE2) receptors given its similarities with SARS-CoV-1.[8-14] ACE2 appears to have a lower expression in children compared to adults,[15] which may explain why disease and neurological complications are less likely in pediatric patients. Neurological involvement may be prompted by a secondary inflammatory response, vascular injury or insult, or immune-related post-infectious disorders.[11] Here we describe 2 adolescent COVID-19 delirium cases that presented to Children's Wisconsin, Milwaukee, Wisconsin in October 2020.

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CASE 1

A 16-year-old African American male with a history of obesity (body mass index [BMI] 38kg/m^2) presented with a 3-day history of altered mental status. Two days prior to his altered mentation, he had rhinitis and congestion for which he took over-the-counter cough medicine and acetaminophen. He also lost his sense of taste and smell but had no fever or cough. He was found talking to himself and staring into the distance for long periods of time. He had not slept for 2 days prior to arrival and had limited oral intake. He then mentioned demons and passive thoughts of suicide, prompting his mother to bring him to the emergency department (ED). He had no prior history of mental illness. He did have a history of intermittent marijuana use (last use 4 days prior to admission) but no other known drug use. He earned mostly As in school, including in advanced placement courses, was active in athletics, and had a healthy social life. Family history includes schizophrenia and bipolar disorder in the maternal grandmother and a cousin suffering from hallucinations of unknown etiology.

On presentation, the patient's vital signs were within normal

limits. He was awake, alert, and looking around the room as if something was there. Initially, he would not speak or follow any commands. There were no gross neurological abnormalities noted other than his mentation. He tested positive for COVID-19 by nucleic acid amplification test (NAAT) via nasopharyngeal swab. Initial laboratory workup was notable for mild transaminitis, an elevated creatine kinase, and elevated creatinine (Table). Remainder of laboratory workup, including inflammatory markers, infectious workup, thyroid workup, and encephalitis evaluation were normal, including a normal cerebrospinal fluid (CSF) profile and neuroimaging (Table). CSF COVID-19 polymerase chain reaction (PCR) was negative, although this test was not yet validated. A urine drug investigation showed marijuana, cotinine, and cough medications (including dextromethorphan), but our toxicologists felt these results did not explain the waxing and waning nature nor duration of altered mentation. Urine tests for synthetic opioids and cannabinoids were negative.

On hospital day (HD) 3, the patient occasionally responded appropriately to questions. He knew his name and the year but not the month. He began to follow simple commands intermittently (open eyes, open mouth, squeeze hand), and exam was frequently interrupted by volitional movements. A 48-hour electroencephalogram (EEG) showed diffuse background slowing suggestive of mild to moderate encephalopathy without epileptiform activity. He continued to have fluctuating episodes of agitation, confusion, delirium, hallucinations, and intermittent unresponsiveness. He frequently required 5-point restraints for acts of self-harm or aggression towards staff and/or family members. He responded well to intramuscular (IM) haloperidol 1-2 mg given as needed for severe agitation but then had decreased alertness and several episodes of dystonia requiring transfer to the pediatric intensive care unit (PICU) on HD 4. His dystonic reaction resolved after several doses of benztropine, but he continued to vacillate between minimal responsiveness and severe agitation punctuated by physical outbursts requiring high levels of sedation and 5-point restraints. His severe agitation led to an increase in his creatinine kinase, which peaked at 3757[iU]/L and decreased appropriately with intravenous (IV) fluids. He required intermittent nasogastric feeds to ensure proper nutrition.

At the peak of his delirium, the patient required frequent doses of benzodiazepines, ketamine, dexmedetomidine, clonidine, olanzapine, and quetiapine, in addition to a continuous infusion of dexmedetomidine. His regimens were adjusted daily in a multidisciplinary effort between psychiatry, neurology, and the PICU. The regimen that proved most efficacious included high doses of quetiapine, clonidine, and melatonin, with haloperidol as a rescue medication. Haloperidol was favored given the deliriogenic nature of ketamine and benzodiazepines and the inefficacy of dexmedetomidine. He began to have periods of lucidity where he was directable, could respond to basic prompts, and feed himself. However, he remained confused about his environment with continued agitation and outbursts. Given his continued encephalopathic presentation, a repeat lumbar puncture was done on HD 8 and CSF was again unremarkable (Table). CSF COVID-19 PCR was again negative as well.

Due to continued concern that his presentation could be due to a COVID-19-related inflammatory process, IV immunoglobulin (IVIG) was administered at 0.4mg/kg of ideal body weight for 5 days on HD 8-12. He showed gradual improvement during this time, although whether his improvement was due to IVIG or optimization of his medication regimen is unclear. He was retested for COVID on HD 11 and was persistently positive.

By HD 13, he was verbalizing more frequently and clearly with extended periods of lucidity but still experiencing confusion, difficulty focusing, and difficulty interpreting stimuli. After transfer back to the acute floor, his agitation decreased, but he became more emotionally labile in which he was often tearful or afraid. Greater periods where he was alert and fully oriented continued to alternate with episodes of paranoid thoughts, delusions, and acts of attempted self-harm. On HD 21, he had a self-resolved period of echopraxia, mutism, staring spell, and posturing suspicious for catatonia. His quetiapine continued to be titrated throughout the admission, ultimately to 700 mg/day in divided doses. He was also on a clonidine transdermal patch 0.3 mg changed weekly, oral clonidine 50 mcg q6 hours and melatonin 20 mg nightly for delirium. Through his admission, he never had significant respiratory involvement, thus was never started on remdesivir or steroids. On HD 25, he was discharged to a psychiatric facility for ongoing medication management. He had a negative COVID-19 test prior to transfer per facility policy.

That evening, he had a temperature of 39.2° C and continued altered mental status and, therefore, was transported back to our pediatric ED where he exhibited evidence of delusions and paranoid psychosis. He was again found to be COVID-19 positive by PCR. The fever resolved after 4 days without any other symptoms or focal signs. During this admission, he continued to have periods of lucidity punctuated by physical outbursts and expressed suicidal ideation, paranoia, ideas of reference, and internal preoccupation. Lorazepam was added to haloperidol and diphenhydramine as part of his rescue regimen to reduce psychotic agitation, with good effect. He was again discharged to a psychiatric facility after a 12-day hospitalization, 36 days after first admission. Delays in discharge were due to the psychiatric facility's hesitancy with his persistent positive COVID-19 tests; however, he did not have respiratory symptoms. On discharge, he was awake, alert, and more interactive. He continued to have paranoia but intermittently answered questions.

The patient spent 12 days in a psychiatric facility with significant improvement and was discharged home 47 days after his initial presentation. Home medications included quetiapine and clonidine, though he self-weaned these medications as his mood improved. During follow-up with primary care 77 days after ini-

Table. Labs and Imaging Results

	Case 1	Case 2
COVID-19 NAAT NP	**HD 2:** + S gene Ct = 31.2, ORF gene Ct = 31.3; **HD 12:** + E gene Ct = 34.6; **HD 23**: -; Readmission: +, S gene Ct = 33.8	Positive
Complete blood cell count	Normal	Normal
Coagulation studies	Normal INR/PT/PTT	NA
Comprehensive metabolic panel: creatinine (ref range 0.5-1.06 mg/dL), AST (ref range 5-35 [iU]/L), ALT (ref range 10-35 [iU]/L)	Glucose 103, creatinine 1.14, AST 89, ALT 90, otherwise normal	AST 37, ALT 38, otherwise normal
Creatinine kinase (ref range 33-145 [iU]/L)	**HD 1:** 1076, peaked on **HD 5** 3757; **HD 16:** 473	NA
C-reactive protein (CRP) (ref range 0-1 mg/dL)	< 0.5 mg/dL	< 0.5 mg/dL
Procalcitonin (ref range < 0.11 ng/mL)	0.20 ng/mL	NA
Erythrocyte sedimentation rate (ref range 0-15 mm)	10 mm	8 mm
Troponin 1 (ref range 0.012-0.034 ng/mL)	< 0.012	NA
Cerebrospinal fluid (CSF)		
Counts	**HD 3:** TNC 2, RBC 0, neutrophils 1%, lymphocytes 85%, glucose 58, protein 16; **HD 9:** TNC 0, RBC 0, glucose 76, protein 17	**HD 2:** TNC 0, RBC 81, protein 25
Culture	Negative x2	Negative
Meningoencephalitis NAAT[a]	NA	Negative
Varicella-zoster virus IgM antibody	NA	Negative
Autoimmune encephalitis panel (CSF)	**HD 3 and 7:** negative	Negative
Neurotransmitter metabolites	**HD 9:** normal	NA
Neopterin (ref range 8-28)	**HD 9:** 17	NA
COVID NAAT	**HD 3 and 7:** negative	Negative
Additional Infectious		
Respiratory polymerase chain reaction panel[b]	NA	Positive for COVID-19, otherwise negative
Epstein-Barr virus IgG	+ IgG, - IgM consistent with past infection	+ IgG, - IgM consistent with past infection
HIV	Negative	Negative
Lyme Ab blood	NA	Negative
Tickborne panel NAAT[c]	NA	Negative
Immune/Thyroid		
Antinuclear antibody titer (ref range < 40)	NA	< 40
Autoimmune encephalitis panel (blood)	**HD 3:** negative	NA
Thyroid studies	Normal TSH, negative thyroid peroxidase Ab	Normal TSH, negative thyroid peroxidase Ab, thyroglobulin Ab
Toxicology		
Serum drug screen	**HD 2:** acetaminophen, doxylamine	NA
Urine drug screen	**HD 2:** positive for marijuana (THC 30 ng/mL), cotinine, acetaminophen, dextrorphan, doxylamine, dextromethorphan, diphenhydramine, negative for ethanol, methamphetamine	H**D 2:** positive for acetaminophen, lidocaine, quetiapine, citalopram, ibuprofen; negative for THC, ethanol, methamphetamine
Urine synthetic opioids	**HD 9:** negative	NA
Urine cannabinoids	**HD 9:** negative	NA
Imaging/Procedures		
Electrocardiogram	**HD 1:** normal	**HD 14:** Sinus tachycardia, otherwise normal
Brain MRI with and without contrast	**HD 2:** normal	**HD 2:** No acute intracranial abnormality. Unchanged subcortical linear T2 FLAIR hyperintensity the mid-left temporal lobe likely represents gliosis surrounding a developmental venous anomaly. Globes normal. Intraorbital optic nerves mildly tortuous, representing a nonspecific finding
Echo, transthoracic, obtained to evaluate for MIS-C	**HD 16:** normal	NA
Electroencephalogram (EEG)	**HD 3:** mild-moderate slowing of the background suggestive of a mild-moderate encephalopathy; HD 7: EEG indicative of mild diffuse cerebral dysfunction (encephalopathy), improved from prior	**HD 2:** normal; **HD 10:** excess beta activity that could be secondary to sedative/hypnotic medications

Abbreviations: NAAT, nucleic acid amplification test; NP, nasopharyngeal; HD, hospital day; Ct, cycle threshold; INR, international normalized ratio; PT, prothrombin time; PTT, partial prothrombin time; NA, not applicable; AST, aspartate aminotransferase; ALT, alanine transaminase; TNC, total nucleated count; RBC, red blood cell; Ig, immunoglobulin; TSH, thyroid stimulating hormone; THC, tetrahydrocannabinol; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; Echo, echocardiogram; MIS-C, multisystem inflammatory syndrome in children.

[a]Tests NAAT for: *Escherichia coli* K1, *Haemophilus influenzae*, Listeria monocytogenes, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, HSV 1 and 2, HHV-6, parechovirus, varicella, and *Cryptococcus neoformans/gatti*.

[b]Tests NAAT for adenovirus; coronavirus-229E, -HKU1, -NL63, and -OC43; novel coronavirus; human metapneumovirus; rhinovirus/enterovirus; influenza A and B; parainfluenza 1, 2, 3, and 4; RSV, *Bordetella pertussis*; *Bordetella parapertussis*; *Chlamydophila pneumoniae*; and *Mycoplasma pneumoniae*.

[c]Tests NAAT for *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia miyamotoi*, *Babesia duncani*, *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, *Ehrlichia canis*, *Babesia divergens*, *Babesia* MO-1, *Ehrlichia muris eauclairensis*.

tial presentation, the patient and his mother reported his mood was significantly better, with no hallucinations or suicidal or homicidal thoughts. He was eating and drinking normally and having no issues with sleep. He reported generally being happy and stress-free. He was attending group therapy weekly and doing well in school.

CASE 2

A 17-year-old White male with high-functioning autism spectrum disorder and anxiety presented with 2 days of worsening altered mental status. At baseline, he had significant anxiety but was able to perform the majority of his activities of daily living independently and clearly communicate his needs. He was taking escitalopram and buspirone, with recent adjustments in both medications per his outpatient psychiatrist. Per his parents, he had become mentally altered over the course of 48 hours. He initially was less interactive with his parents and ruminated on bizarre ideas, such as building a piano. He progressed to having visual and auditory hallucinations, bursts of inappropriate laughter, poor eye contact, abnormal but nonrepetitive hand movements, limited oral intake, and inappropriate urination. He lost his sense of taste and smell. After >24 hours without sleep, his parents sought medical evaluation.

On admission, the patient had normal vital signs and physical exam, except for an elevated blood pressure and his neurologic and mental status exam. He had nonpurposeful, nonrhythmic upper extremity movements and was able to follow some simple commands but not consistently. He interacted minimally, predominantly using echolalia—vocalizing to "parrot" words he was hearing. He was able to ambulate without falling, although he appeared somewhat unsteady on his feet and needed assistance. On HD 1-3 he was described as "euphoric," with pressured speech and grandiosity, bouts of agitation, talking in nonsensical phrases, laughing inappropriately, yelling random words, and using loud profanity-laden language, which was not his baseline.

Serotonin syndrome was considered given recent adjustments to psychiatric medications, but his exam was inconsistent with this and symptoms did not improve with cessation of home medications. Drug screen was consistent with prescribed medications. A COVID-19 NAAT was positive. Laboratory workup, including complete blood count, comprehensive metabolic panel, inflammatory markers, thyroid studies, and encephalitis evaluation, were unremarkable, including a normal CSF profile (Table). Magnetic resonance imaging (MRI) demonstrated known unchanged subcortical linear T2 fluid-attenuated inversion recovery (FLAIR) hyperintensity in mid-left temporal lobe attributed to gliosis surrounding a developmental venous anomaly but no other intracranial abnormalities. CSF COVID-19 PCR was negative. Short-term EEG on HD 2 was normal.

Given concerns for COVID-19 delirium, melatonin and quetiapine were started in addition to behavioral interventions for delirium. His symptoms waxed and waned but showed gradual improvement. Melatonin was started at 5mg and increased to 10 mg several days later. The quetiapine dose was increased gradually in the first week of hospitalization. He showed improvements in his interaction with parents and voiding behaviors, but he continued to speak in nonsensical sentences and exhibited hallucinations. He required several as-needed doses of quetiapine and IM haloperidol due to behavioral outbursts (agitation, shouting, spitting, throwing, and hitting his mother once), but he never required physical restraints. He also required IV hydration for poor fluid intake for the first few days of admission.

By HD 8, he was still delirious, pacing around his room, babbling, and had intermittent tic-like movements and facial grimacing with headshaking. He put nonfood items in his mouth, like string and pieces of plastic. When called by his name, he would often refer to himself by another name, such as his friend's name. Repeat EEG was done on HD 9 and showed excess beta activity, likely secondary to quetiapine sedative effects, but was otherwise normal without change in semiology. On HD 10, he was started on guanfacine extended release (ER) 1 mg each morning. By HD 11, the quetiapine dosage was 350 mg/day divided 3 times per day. He started having more coherent sentences, knowing his name, recognizing some staff members, properly used utensils and dishes, and had improved fluid intake. By HD 13, he was answering questions more appropriately and was much more redirectable by his mother. He still had moments of yelling and nonsensical speech but was interacting more appropriately with people in his room.

He was discharged home on HD 14 after continued small improvements in his mental status and parental comfort in safely caring for him at home. He was oriented to self, parents, and birth date, though not to his age or location. He continued to have generally nonsensical speech but would answer direct questions with complete and more coherent sentences. He was discharged on melatonin 10 mg nightly, guanfacine ER 1mg daily, quetiapine 100 mg in the morning and noon and 150 mg at bedtime, and quetiapine 50 mg daily as needed, with plans to follow closely with his outpatient psychiatrist. His symptoms continued to improve slowly with near resolution of hallucinations and more consistent self-orientation. However, 43 days after his admission, he continued with disordered thoughts and paranoia but improving nutritional intake.

DISCUSSION

We highlight 2 adolescent males with persistent delirium symptoms after COVID-19 infection. Both suffered from anosmia and ageusia but lacked significant respiratory symptoms. Other organ systems showed no sign of dysfunction, and steroids were not used. We believe these are the first reported cases of COVID-19-associated delirium in children outside of multisystem inflammatory syndrome in children (MIS-C).

Delirium has emerged as a prevalent but likely underdetected

manifestation of COVID-19. Among 71 adults with COVID-19, mostly admitted to the intensive care unit, 42% met DSM-IV criteria for delirium.[16] Another study reported on 10 adult patients with confirmed or probable COVID-19 who developed encephalopathy with features of delirium and psychosis; workup including MRIs and CSF analysis were largely unrevealing and most recovered at discharge.[4] In 1 case report, a 55-year-old woman developed delirium with slow improvement and recovery by day 52 of illness,[17] which follows a similar timeline in our patients.

Delirium has significant morbidity in pediatric patients, and it is critical to diagnose rapidly in order to discern its etiology and determine management.[18] Children with developmental delay and family history of delirium appear to be at higher risk for delirium. Emotional lability, hallucinations, depression, and anxiety have been reported in children with SARS-CoV-1.[19] Encephalitis and seizures in children with COVID-19 have been reported; however, delirium has only been reported in MIS-C.[10,11,20,21] A 14-year-old boy with MIS-C developed hyperactive delirium requiring physical restraints, haloperidol, lorazepam, and dexmedetomidine,[22] similar to Case 1. His evaluation of delirium was complicated by ionotropic support, anakinra, and steroids for MIS-C; he made a full recovery. Four children with MIS-C in a United Kingdom hospital developed encephalopathy; all cases resolved.[23]

The management of delirium associated with COVID-19 poses additional challenges given the lack of evidence-based guidelines and difficulty performing nonpharmacologic interventions under heightened isolation requirements.[24,25] The foundation of our treatment strategy for addressing symptoms of delirium, agitation, and psychosis was the triad of alpha-2 agonists (clonidine, dexmedetomidine, guanfacine), neuroleptic agents (quetiapine, haloperidol, olanzapine), and melatonin.[2,26] Dexmedetomidine and clonidine have a significant history of being effective agents in the treatment of hyperactive delirium. A dopamine agonist can be used if there is concern for akinetic mutism or catatonia but should be used with caution in delirium.[26-28] If patients display violence toward self or health care providers, faster titration of antipsychotics may be indicated.[29] IVIG also has been trialed with success[30] and may have helped in Case 1.

Recent literature suggests a positive role for guanfacine, especially with its lower cardiovascular effects compared to clonidine.[31] The extended-release formulation of guanfacine eliminates the potential for rebound hypertension/tachycardia that could be seen with oral clonidine or guanfacine. We preferred second generation/atypical neuroleptic agents because of their lower potential for both dystonias/extrapyramidal side effects and QTc prolongation. We chose the low-potency D2 blockade agent quetiapine (which probably has the broadest range of experience of atypical antipsychotics in treating pediatric delirium) rather than a high-potency D2 blockade agent (such as olanzapine or haloperidol) out of concern for catatonic-like symptoms and abnormal movements that could have represented dopamine-depletion symptoms. Olanzapine and haloperidol were used only when a rapid-response IM agent was necessary.

Melatonin has long been a therapeutic staple for restoring and maintaining the sleep-wake cycle that is often disrupted in delirium. It has antioxidant properties, eliminating free radicals to a much greater degree than vitamin C and E, anti-inflammatory and immunoregulatory effects, cytoprotection and neuroprotection benefits, and some indirect evidence of possible antiviral effects.[32-34] Several recent studies have suggested that melatonin may have antiviral action towards COVID-19. While there is no clear guidance in the literature regarding dosage, dosing above chronobiotic benefit has been proposed—up to 36-100 mg per day.[32,35,36]

Multiple psychiatric medication classes have been used to treat delirium in the setting of COVID-19, and close follow-up care is warranted for patients. However, the COVID-19 pandemic has disrupted the normal process of obtaining psychiatric care, with many routine services limited or closed.[37] Many psychiatric programs also have adjusted enrollment criteria during the pandemic, which may delay or deny acceptance until the patient recovers.[38] Meanwhile, virtual modalities for providing follow-up care have increased.[38] Because of these limitations on follow-up, discharge planning required involvement from inpatient psychiatry, case management, social work, and the family.

As our understanding of COVID-19 rapidly evolves, we should be aware of the possible pediatric neuropsychiatric complications, including delirium, and the potential management strategies and discharge challenges that may emerge in these patients.

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