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We present 4 pediatric patients with trisomy 21 (T21) and associated comorbidities who developed coronavirus disease 2019 requiring hospitalization. A review of the literature revealed that comorbidities associated with T21 may predispose patients to severe disease. Children with T21 should be considered high risk and monitored carefully if infected with severe acute respiratory syndrome coronavirus 2. (J Pediatr 2021;228:294-6).

Case 1

A 17-year-old male patient with T21, congenital heart disease (CHD), and obesity presented to our emergency department (ED) after 5 days of severe throat pain, nonproductive cough, and poor oral intake secondary to pharyngitis, but without breathing difficulty. He was febrile but had a normal respiratory examination, including normal work of breathing. A rapid strep test and SARS-CoV-2 PCR were sent; both were positive. Because of overall mild symptoms, he was discharged home to receive amoxicillin for streptococcal pharyngitis. Three days later, he returned to the ED because of dehydration, fever, and concern for increasingly difficult breathing with mild supraclavicular retractions. His chest radiograph showed bilateral lower lobe reticulonodular opacities with focal airspace opacities in the left-mid-to-lower lobe and he was hospitalized for further care. On hospital day of admission, day 1, he had intermittent oxygen desaturation to 85% while asleep which resolved with re-positioning. On day 2, he required 2 L oxygen by nasal cannula for labored work of breathing, tachypnea, accessory muscle use, and persistent hypoxemia. Hydroxychloroquine was initiated while awaiting approval of emergency use of investigational new drug for remdesivir. On day 4, he was transferred to the intensive care unit because of increasing tachypnea and need for supplemental oxygen and was started on intravenous remdesivir (200 mg intravenous loading dose on day 1, then 100 mg intravenous daily on days 2-10). Hydroxychloroquine was discontinued. Intubation was required on day 5. On day 10, he had an increase in C-reactive protein from 3.2 mg/dL at admission to 7 mg/dL and procalcitonin from 0.14 at admission to 2.43, as well as new onset of hypotension to 60/40 mm Hg. To combat his hyperinflammatory state, tocilizumab was started. His C-reactive protein and procalcitonin decreased after a single dose to 2.7 mg/dL and 1.25, respectively. On day 14, he was extubated, maintained on high-flow oxygen by nasal cannula and was no longer febrile. After extubation, he required continuous positive airway pressure at night time for probable obstructive sleep apnea (OSA). He was discharged to home on day 23 after requiring no oxygen supplementation during the daytime.

Case 2

A 10-month-old male child with T21, CHD, pulmonary hypertension, OSA, and dysphagia was brought to medical attention with a 1 day history of fever to 38.1°C, productive cough, and increased work of breathing. On examination he was afebrile, without increased work of breathing; auscultation of his chest revealed clear breath sounds bilaterally. A chest radiograph showed bilateral lower lobe reticulonodular opacities with focal airspace opacities in the left-mid-to-lower lobe and he was hospitalized for further care. On hospital day of admission, day 1, he had intermittent oxygen desaturation to 85% while asleep which resolved with re-positioning. On day 2, he required 2 L oxygen by nasal cannula for labored work of breathing, tachypnea, accessory muscle use, and persistent hypoxemia. Hydroxychloroquine was initiated while awaiting approval of emergency use of investigational new drug for remdesivir. On day 4, he was transferred to the intensive care unit because of increasing tachypnea and need for supplemental oxygen and was started on intravenous remdesivir (200 mg intravenous loading dose on day 1, then 100 mg intravenous daily on days 2-10). Hydroxychloroquine was discontinued. Intubation was required on day 5. On day 10, he had an increase in C-reactive protein from 3.2 mg/dL at admission to 7 mg/dL and procalcitonin from 0.14 at admission to 2.43, as well as new onset of hypotension to 60/40 mm Hg. To combat his hyperinflammatory state, tocilizumab was started. His C-reactive protein and procalcitonin decreased after a single dose to 2.7 mg/dL and 1.25, respectively. On day 14, he was extubated, maintained on high-flow oxygen by nasal cannula and was no longer febrile. After extubation, he required continuous positive airway pressure at night time for probable obstructive sleep apnea (OSA). He was discharged to home on day 23 after requiring no oxygen supplementation during the daytime.
at home (required overnight) to 2 L because of intermittent oxygen desaturation to 85%. Symptoms progressively worsened, including increased work of breathing and decreased oxygen saturation, requiring escalation of support by high flow oxygen by nasal cannula. Vancomycin was initiated when he developed fever. On day 2, positive SARS-CoV-2 was known, and his antibiotics were discontinued. On day 4, he was weaned to oxygen by regular flow nasal cannula in the morning and placed back on home O2 of 0.75 L overnight. He tolerated being on absence of daytime supplemental O2 on day 5 and was discharged to home.

Case 3

A 15-year-old male patient with T21, OSA, CHD, dysphagia, and recurrent aspiration pneumonia was brought to the ED after 2 days of cough, 1 day of fever, and recurrent nonbilious, nonbloody emesis following gastrostomy tube (G-tube) feeding. Examination revealed temperature of 38.8°C and tachycardia, initially with normal oxygen saturation and no increased work of breathing. Oxygen desaturation to 86% ensued and requiring supplementation via nasal cannula; his chest radiograph showed no focal consolidation. During hospital day 1, he required escalation of flow to a maximum of 2.5 L. On day 2, he was re-started on continuous G-tube feedings and subsequently was weaned to room air. On day 4, feeding regimen was resumed to home bolus, and he was discharged to home.

Case 4

A 14-year-old male patient with T21, obesity, CHD, and OSA had the acute onset of refusal to eat, abdominal pain, dry cough, and fatigue. He did not have emesis, diarrhea, increased work of breathing or fever, and remained stable on his home settings of continuous positive airway pressure without supplementary oxygen. Per home testing, his blood glucose was 53, and his father brought him to an outside hospital ED for further care. He was given fluids and an anti-emetic and underwent an abdominal computed tomography for continued abdominal pain. Although the abdomen appeared normal on computed tomography, the bases of the lungs showed ill-defined mixed airspace opacities in the lower lobes and inferior aspect of the lingula. SARS-CoV-2 PCR was sent and was positive. He was transferred to our institution for care and monitoring during which time he remained stable without fever, increased work of breathing, or need for supplementary oxygen. He was discharged after 1 day of hospitalization.

Discussion

Children with intellectual and developmental disability, including those with T21, had increased mortality rates from COVID-19 compared with peers without intellectual and developmental disability. The anatomic, immunologic, and metabolic comorbidities associated with T21, as present in our cases, may increase their risk for severe COVID-19. Children with T21 have abnormal upper airway phenotypic features including macroglossia, midface hypoplasia, choanal stenosis, narrow nasopharynx, enlarged tonsils and adenoids, lingual tonsils, and shortening of the palate, all of which can exacerbate patency of airways during respiratory infections. These abnormalities plus generalized hypotonia and increased likelihood of obesity, increase the prevalence of sleep–disordered breathing among this population, with estimated rates varying from 31% to 79% in children with T21. The onset of sleep–disordered breathing in children with T21 typically occurs at a younger age, after the second to third year of life, compared with children without T21.

Children with T21 also have a high rate of CHD. Structural cardiac defects are found in about 40% of children

### Table. Characteristics of patients with T21 and COVID-19

| Tests/cases | Comorbidities | Type of CHD | Pulmonary Hypertension | Symptomatic System | WBC × 10³ cells/µL | CRP mg/dL | Procalcitonin ng/mL | Ferritin ng/mL | D-Dimer mcg/mL | Symptomatic Days PTA | Days Hospitalized | Max Resp Support | BMI | Therapy |
|-------------|---------------|-------------|------------------------|-------------------|-------------------|-----------|-------------------|----------------|----------------|-------------------|----------------|-----------------|-----|---------|
| 1           | OSA, Obesity, CHD | Ventricular septal defect s/p repair | No | Respiratory, ENT | 4.15 | 1.3 | 0.10 | 527 | 2.26 | 8 | 23 | Mechanical Vent | 35.38 |
| 2           | CHD, OSA, Dysphagia | Tetralogy of Fallot, s/p repair | Yes | Respiratory | 9.14 | 1.3 | 1.08 | 587 | - | - | 7 | HFNC | 15.6 | HCQ (3 days only), Toci, Rem |
| 3           | OSA, CHD, dysphagia, epilepsy, hypothyroid, recurrent aspiration pneumonia | Atrial septal defect s/p repair | No | Respiratory, GI | 4.3 | 6.2 | - | - | - | 3 | 4 | NC | 22.2 |
| 4           | OSA, CHD, obesity | Atrial septal defect s/p repair | No | GI | 1.46 | 1.2 | - | <0.10 | 117 | 1 | 2 | Baseline Support | 28.3 |

BMI: body mass index; CRP, C-reactive protein; ENT, ear, nose, and throat; GI, gastrointestinal; HCQ, hydroxychloroquine; HFNC, high flow nasal cannula; PHTN, pulmonary hypertension; PTA, prior to admission; NC, nasal cannula; Rem, remdesivir; Toci, tocilizumab; WBC, white blood cells.
with T21, most commonly seen are atrioventricular septal defects. Children with T21 and atrioventricular septal defects more frequently develop pulmonary vascular hypertension compared with those without trisomy. For children with T21, the interplay between complicated respiratory and cardiovascular anatomy and pathophysiology likely lead to increased severity and mortality of respiratory infections. Krishnan et al highlighted the interplay between CHD, pulmonary hypertension, and T21 as it relates to SARS-CoV-2 infection; 60% of patients with pulmonary hypertension and SARS-CoV-2 infection requiring hospitalization also had T21 and atrioventricular septal defects. Among our 4 cases, all patients had repaired CHD, though only 1 had pulmonary hypertension.

Children with T21 may have abnormal immune function that predisposes them to more severe infections, prolonged lower respiratory tract infections, and increased incidence of acute lung injury. Studies have found variations in immune functions in children with T21 including: mild to moderate T- and B-cell lymphopenia, with marked decrease of naive lymphocytes; impaired mitogen-induced T-cell proliferation; reduced specific antibody responses to immunizations; and defects of neutrophil chemotaxis. In addition, the number of CD14/16+ proinflammatory monocytes is higher in patients with T21 relative to a low absolute monocyte count, exacerbating inflammatory morbidity during infection.

Obesity has emerged as a primary risk factor for severe COVID-19. Previous studies estimate an increased prevalence of obesity among children with T21. A meta-analysis by Bertapelli et al found the worldwide prevalence of overweight children with T21 to be 23%-70%, with obesity ranging from 0% to 63%. Current studies propose the following hypotheses: increased leptin level thought to be related to leptin resistance and decreased satiety, lower resting energy expenditure, and lower physical activity compared with youth without T21. Increased weight can lead to upper airway obstruction and obstructive sleep apnea, which is compounded by anatomic differences in children with T21.

Obesity also can lead to immune dysregulation, increasing the severity of viral disease. Obesity can result in a state of chronic meta-inflammation, which can blunt antiviral response of the host. During the 2009 H1N1 pandemic, obesity was associated with increased hospitalization and mortality. Children with T21 have hyperactivation of their interferon signaling, ultimately resulting in a hyperinflammatory state. For SARS-CoV-2 infection, there is increasing evidence that a hyperinflammatory response to the virus leads to increased morbidity and mortality. Children with T21 may be at increased risk for further upregulation of proinflammatory cytokines during COVID-19.

The unique risks of upper and lower respiratory abnormalities, immune defects, increased rates of obesity, and sleep disordered breathing all place those with T21 at higher risk for severe disease from respiratory pathogens. It seems prudent to take caution with children and adults with T21 infected with SARS-CoV-2. ■

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