SARS-CoV-2 Infection in Patients with Down Syndrome, Congenital Heart Disease, and Pulmonary Hypertension: Is Down Syndrome a Risk Factor?

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With increasing information available about the epidemiology, pathophysiology, and management of patients affected with severe acute respiratory syndrome corona virus-2 infection, patients with Down syndrome, congenital heart disease, airway obstruction, and pulmonary hypertension present a unique challenge. This case series describes 3 patients with Down syndrome and respiratory failure secondary to coronavirus infection. *(J Pediatr 2020;225:246-8).*

Since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was first described, the disease has become a global pandemic. Through May 2020, it has affected more than 3.6 million people worldwide and left more than 251 000 dead. In the 4 months since it was first described, there has been increasing understanding about the epidemiology, populations at risk, pathophysiology, possible treatment opportunities, and research into the development of a vaccine.[1,2]

It has been observed that adults with pulmonary hypertension who otherwise have minimal cardiopulmonary reserve may not fare worse with SARS-CoV-2 than the general population.[3,4] Another subgroup of patients, those with congenital heart disease (CHD), is a population being closely followed in several adult CHD registries.[5]

We report 3 patients with Down syndrome and World Symposium of pulmonary hypertension group 1 pulmonary hypertension associated with CHD who were hospitalized with SARS-CoV-2 illness in April 2020. They are unique in that a combination of Down syndrome, CHD, obstructive sleep apnea (OSA) and pulmonary hypertension as comorbidities typically puts them at high risk during respiratory viral illnesses.[6,7] This report is covered under the Columbia University Institutional Review Board protocol AAAT0074 approval effective April 24, 2020 (COVID in Patients with Congenital Heart Disease Protocol Version #: 1).

Case 1

A 3-year-old boy with Down syndrome, repaired atrioventricular septal defect (AVSD), and pulmonary hypertension was admitted because of fever, cyanosis, and lethargy. His comorbidities include OSA with dependence on continuous positive airway pressure (CPAP), and hypoxic ischemic encephalopathy with seizures. His pulmonary hypertension secondary to Down syndrome, OSA, and chronic lung disease from recurrent severe viral illnesses previously had been severe, but over the year before the current admission, he had mild pulmonary hypertension and remained on sildenafil as monotherapy. He has a prior history of multiple hospitalizations for viral bronchiolitis requiring mechanical ventilation and a cardiopulmonary arrest necessitating prolonged resuscitation and extracorporeal membrane oxygenator support.

During the current admission, he had extensive airspace disease, consolidation, and pneumonia on chest radiography and computed tomography scanning. Polymerase chain reaction testing of nasopharyngeal secretions was positive for SARS-CoV-2, and laboratory test results showed D-dimers, C-reactive protein, and the erythrocyte sedimentation rate to be elevated. Serum IL-6 levels, complete blood count, serum hepatic enzymes, troponins, ferritin, procalcitonin, and pro b-type natriuretic peptide levels were normal. He was initially treated with antibiotics for urosepsis and also received 2 days of methylprednisone, azithromycin, and hydroxychloroquine, which were terminated after 48 hours because of prolongation of the QTc interval on electrocardiogram. An echocardiogram showed normal biventricular function with mild pulmonary hypertension. After 3 days of hospitalization, he developed mild hypotension and was obtunded, prompting further sepsis evaluation, escalation of antibiotics and increase in CPAP from 5 to 8 cm H_2O. His baseline regimen of sildenafil 10 mg 3 times a day was continued. He has since recovered to baseline and is doing well at home.

AVSD	Atrioventricular septal defect
CDH	Congenital heart disease
CPAP	Continuous positive airway pressure
OSA	Obstructive sleep apnea
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2

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Case 2

A 25-year-old woman with Down syndrome, unrepaired AVSD with Eisenmenger physiology and OSA, dependent on night CPAP, was previously followed as an outpatient and treated with sildenafil 40 mg 3 times a day. She had a telemedicine consultation, during which her parents reported that she had high fever, emesis, decreased urine output, and lethargy. She was assessed to be dehydrated, and was hospitalized for rehydration and further management. She was hypotensive and hypoxemic on admission, and nasopharyngeal secretions tested positive by polymerase chain reaction for SARS-CoV-2. Her D-dimer was mildly elevated, as were C-reactive protein and lactate dehydrogenase, with normal procalcitonin and troponin levels. Chest radiography revealed bilateral fluffy infiltrates. She was admitted to the intensive care unit for fluid resuscitation and respiratory management. She was treated with oxygen via face mask and hydroxychloroquine and azithromycin for 5 days. She did not require invasive ventilation. On day 3 of hospitalization, she was enrolled in a randomized, placebo-controlled clinical trial with sarilumab, an IL-6 receptor antagonist. She responded well to therapy and was discharged after 8 days. She remains stable at home on her baseline medications and night-time CPAP.

Case 3

A 21-year-old man with obesity (body mass index of 48) with Down syndrome and OSA had an unrepaired partial AVSD with a small primum atrial shunt and no ventricular shunt. A cardiac catheterization at 6 years of age had indicated minimal atrial shunting and mild pulmonary hypertension, which was attributed to OSA, for which night-time CPAP was recommended. At 19 years of age, he was reevaluated for worsening dyspnea. Echocardiography and cardiac catheterization revealed systemic right heart pressures with minimal atrial shunting and an indexed pulmonary vascular resistance of 17 Wood units*square meter.[2] He was treated as an outpatient with ambrisentan and tadalafil for pulmonary hypertension. He was taken to his primary care doctor with a cough, with several known ill contacts, and was diagnosed with pneumonia. Azithromycin and hydroxychloroquine were prescribed and administered for 3 days when therapy was stopped owing to prolongation of the QTc interval. Because of worsening shortness of breath, fever, and cough, he was admitted, and had nasopharyngeal secretions positive for SARS-CoV-2 by polymerase chain reaction. Oxygen saturation fell into the 70% range from a baseline of 92%, despite 20 L of oxygen delivered via high-flow nasal cannula. He was intubated and diagnosed with SARS-CoV-2 pneumonia-associated respiratory failure. Ambrisentan and tadalafil were continued for pulmonary hypertension. He was given ceftriaxone intravenously and inhaled nitric oxide with improved oxygen saturation. He also received a dose of tocilizumab as part of a clinical trial. The intensive care team used strategies for acute respiratory distress syndrome, including prone ventilation with gradually improving ventilatory requirements. During hospitalization, he received a tracheostomy and has since been discharged home on tracheostomy collar by day and night time CPAP.

Discussion

Patients with Down syndrome and CHD generally are considered at higher risk for developing viral infections and often have significantly increased morbidity and mortality.[5-9] In patients with adult CHD, those with unrepaired shunts and Eisenmenger physiology usually are at higher risk for developing more severe disease with viral infections such as SARS-CoV-2.[5] A large number of pediatric and adult patients with pulmonary hypertension are followed at the Pulmonary Hypertension Center at Columbia University Medical Center in New York City, which has the highest incidence of SARS-CoV-2 infection in the United States and 3 out of the 5 pulmonary hypertensive patients who required hospitalization had Down syndrome and AVSD, but have all survived.

The immunologic function in Down syndrome patients has been studied extensively.[6-10] Circulating cytokine levels and function reported have been variable, possibly reflecting the ages of the patients studied, their environment and associated disorders as well as previous exposure to infections.[6-10] Patients with Down syndrome have been reported to have increased circulating cytokines including tumor necrosis factor-α, IL-β and IL-γ levels, and altered cell-mediated immune function, which likely cause abnormal inflammatory responses and more severe disease in response to viral infections. Cetiner et al suggest that a poor anti-inflammatory state with low IL-6 and tumor necrosis factor-α may explain the cause of susceptibility to infections in patients with Down syndrome.[10] It has been speculated that repeated viral infections in the first years of life may boost natural humoral and cellular immunity explaining decreasing infections with age. Patients 1 and 2, who had a history of repeated viral infections, had milder clinical courses in response to SARS-CoV-2 infection. Historically, patient 3 did not have frequent viral infections as a child, and had a more severe and prolonged course of SARS-CoV-2 infection.

Although information about the overall epidemiology and clinical characteristics of patients with CHD and SARS-CoV-2 infection is still emerging, patients with Down syndrome should continue to be considered in a high-risk category. Their clinical presentation may be variable depending on the unique alterations to the immune system associated with Down syndrome. ■

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