Radiology

Low-field MRI and ventilation-perfusion mismatch after pediatric COVID-19

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See also the article by Heiss and Tan et al.

The COVID-19 pandemic has resulted in more than 6.4 million deaths worldwide. Age at the time of infection is the most significant determinant of outcome (1). SARS-CoV-2 infection in children and adolescents is generally asymptomatic or mild. In contrast, older adults have high rates of hospitalization and mortality (2). Worldwide, deaths from infection in the pediatric population are also rare, at 0.17 per 100 000 individuals. This comprises only 0.5% of the estimated total mortality from all causes in a normal year (3). Yet, two concerning longer-term consequences of SARS-CoV-2 infection have been described even after mild or asymptomatic infection. The first long-term consequence is multisystem inflammatory syndrome in children. This condition is an immune-mediated disease that occurs in fewer than 0.1% of children 2 to 6 weeks following COVID-19 infection. The second long-term consequence is long COVID. The label "long COVID" is used to describe persistent symptoms following primary infection affecting the sensory, neurologic, and cardiorespiratory systems as well as mental health.

There is currently no international consensus regarding the definition of long COVID in children or agreement on the duration of symptoms that justify the diagnosis. A multitude of symptoms has been attributed to pediatric long COVID. Many of these symptoms are nonspecific and highly prevalent in the general population. These symptoms include fatigue, loss of appetite, sleep disturbance, concentration difficulties, and muscle or joint pain. The nature and frequency of post-acute sequelae of COVID-19 in children are poorly understood, with no longitudinal studies that report outcomes for recovery. Most studies to date have used questionnaires with self- or parent-reported symptoms without clinical assessment or objective parameters such as pulmonary function testing or imaging. Also, the majority lacked a control group.

Chest imaging has played a central role in the initial diagnosis and monitoring of adult patients with SARS-CoV-2 infection, particularly CT evaluation. The most common manifestations include bilateral, peripheral, ground-glass, and reticular opacities. These abnormalities are mainly located in the lower lobes, frequently accompanied by consolidation. CT angiography has shown endoluminal filling defects in up to 30% of patients, located predominantly within segmental and subsegmental pulmonary arteries. Perfusion abnormalities indicative of extensive microangiopathy have been demonstrated in individuals with persistent respiratory symptoms 3 months after hospitalization for SARS-CoV-2 pneumonia (5). At autopsy, endoluminal clots have been identified in the pulmonary arterial circulation in the absence of apparent embolism. The presence of severe endothelial injury associated with intracellular virus, disrupted cell membranes and widespread capillary microthrombi has also been confirmed (6). In children with COVID-19, parenchymal lung abnormalities at CT are generally less severe than in adults, consisting mainly of ground-glass opacification. However, respiratory symptoms in some pediatric patients following primary SARS-CoV-2 infection are persistent. Also, there is poor specificity of imaging features of pediatric COVID-19 on chest radiography and CT. Thus, there is an interest in exploring alternative imaging approaches that might yield more meaningful functional information while also limiting the need for ionizing radiation and its attendant risks.

To better delineate the anatomical and functional lung abnormalities in pediatric patients with documented prior SARS-CoV-2 infection, Heiss et al. performed a prospective clinical, laboratory, and MRI evaluation of 54 children and adolescents with a history of COVID-19

infection over a 5-month period. Clinical features during and after infection, the time elapsed between a positive reverse transcription polymerase chain reaction (RT-PCR) test and study participation, and laboratory parameters were compared with the imaging results. The study group included 29 recovered patients, 25 patients with long COVID, and 9 healthy volunteers. Long COVID was defined according to the current World Health Organization definition as a persistence of symptoms for a minimum of 12 weeks, and one of four criteria, including 1) symptoms persisting from the time of acute infection or treatment; 2) symptoms resulting in a new health limitation; 3) new symptoms developing after acute infection but believed to be a consequence of COVID, and 4) worsening of a pre-existing underlying medical condition. None of the patients with COVID-19 was hospitalized during the acute phase of infection. The median interval between diagnosis and study participation was 222 ±134 days.

Low-field MRI was used for the depiction of lung morphology and for the determination of ventilation and perfusion. Low-field MRI is associated with greater field homogeneity than the usual high-field MRI systems used for clinical imaging. Thus, low-field MRI results in decreased image distortion with improved image quality at the air-tissue interfaces of the lung (7). Studies were performed with a free-breathing technique. Coronal and transverse images were acquired with respiratory gating for morphological evaluation. The functional assessment included the determination of regional pulmonary ventilation and perfusion. The percentage of areas with and without defects was calculated on both ventilation and perfusion maps.

Of the 54 patients with a history of SARS-CoV-2 infection, 30% reported shortness of breath and 28% complained of dyspnea. However, only a single patient in the recovered group

had morphological changes that consisted of minor linear atelectasis at both lung bases. All the other recovered patients and patients with long COVID had morphologically normal lungs. In sharp contrast, there was reduced ventilation and perfusion (V/Q) matching in both the recovered patient group (62 ± 19%; *P*=.006) and patients with long COVID (60 ± 20%; *P*=.003) compared with the healthy controls (81±6.1%). This reduction in V/Q matching compared with the healthy controls was identified in patients at less than 180 days from the time of primary infection, as well as between 180 and 360 days.

There is little available data documenting alterations in respiratory function following primary SARS-CoV-2 infection in children. In a report by Ashkenazi-Hoffnung et al. of 90 pediatric patients evaluated at a median of 112 days after COVID-19 diagnosis, chest radiographic abnormalities were seen in 12, including infiltrates, peribronchial thickening, and an interstitial pattern. Abnormal pulmonary function tests were documented in 27 of 60 children (45%) consistent with mild obstruction and air trapping on lung volume evaluation. Although radiologic and spirometric changes were mild, they were observed in more than half of the patients, lending support to the importance of long-term pulmonary evaluation (8). A case report by Buonsenso et al. described a 14-year-old girl with long COVID who demonstrated signs of pulmonary hypertension on exercise testing without evidence of ventilation-associated impairment (9). Lung scintigraphy was performed with technetium-99m macroaggregated albumin as the perfusion tracer, followed by SPECT with co-registered CT acquisition. A perfusion defect was identified in the right upper lobe without an associated lung parenchymal abnormality on CT. These results suggested the possibility of endothelial and microvascular damage as previously documented in adults with COVID-19 at autopsy. Studies of adults

following acute COVID-19 using inhaled hyperpolarized xenon-129 MRI have also revealed pulmonary functional and vascular abnormalities, including in younger patients with few comorbidities (10).

Limitations of the study by Heiss et al. include a patient selection bias, where families of children with symptomatic acute or post-acute COVID-19 were more likely to seek enrollment in the study than those with a relatively mild course of the disease. A reference standard such as ventilation-perfusion scintigraphy or pulmonary function testing is lacking and there is no longitudinal data.

In conclusion, information regarding the long-term effects of COVID-19 in children and adolescents is scant, and current patient management is heavily influenced by clinical experience in adults. Although respiratory system manifestations of acute COVID-19 are typically mild in children, the longer-term impact of the disease on lung function is poorly understood. The ability of low-field MRI to noninvasively depict lung perfusion abnormalities without the need for ionizing radiation holds great promise in understanding the underlying pathophysiological mechanisms of COVID-19 in children and adolescents. This should ultimately lead to improved diagnostic and therapeutic approaches specifically tailored to the pediatric population.

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Author biography

Dr. Paltiel is the Director of Ultrasound at Boston Children's Hospital, an associate editor of *Radiology*, Chair of the Publications Committee of the Society for Pediatric Radiology, and the editor, with Edward Y. Lee, of the textbook *Pediatric Ultrasound*. She has been a principal investigator of research grants awarded by the National Institutes of Health and the United States Department of Defense for work on US contrast material.

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