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Reversible peripheral airway obstruction and lung hyperinflation in children presenting with dyspnea and exercise intolerance after COVID-19 infection

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Clinical Implications

The majority of children who develop persistent dyspnea after COVID infection exhibit reversible peripheral airway obstruction and lung hyperinflation despite normal spirometry. These children improve with daily inhaled corticosteroid and bronchodilator therapy.

Children infected with coronavirus 2 (SARS-CoV-2) infection generally report milder symptoms compared with the more acute symptoms of adults;[1] however, a subset experience persistent symptoms after infection. The most prominent symptoms of "long-coronavirus disease 2019" (COVID) are psychological symptoms and dyspnea that can significantly affect quality of life by limiting daily activities.[2-4] The pathophysiology of post-COVID pediatric dyspnea is not well described, and the lack of objective criteria may lead some practitioners to assume a psychological trigger, especially when spirometry values are normal. From a study approved by the BRANY institutional review board, we present a child without previous respiratory symptoms who developed post-COVID dyspnea. Despite normal spirometry, testing with impulse oscillometry (IOS) demonstrated peripheral airway obstruction that reversed with albuterol, and plethysmography testing revealed lung hyperinflation. Over the next few months, his symptoms and airway obstruction improved with daily inhaled corticosteroid and bronchodilator therapy.

The patient was a 17-year-old Hispanic boy who presented for evaluation of post-COVID dyspnea. He had developed symptomatic COVID in November 2020—before a vaccine was available—which was confirmed with a rapid antigen test. Symptoms began with a sore throat; the next day he began to experience chest tightness, coughing, myalgias, and abdominal pain. Over the next 3 weeks after infection, he developed severe shortness of breath and decreased exercise tolerance, which continued over the next 5 months. His primary physician prescribed fluticasone metered-dose inhaler (MDI) 110 and albuterol MDI and then switched to fluticasone/salmeterol (Advair) 115 MDI, but he was poorly adherent to this regimen and took his inhalers without a spacer. Nevertheless, he noted some improvement in exercise tolerance when taking these medications so that he was able to walk on the treadmill for 5 minutes before becoming short of breath.

This patient had never been diagnosed with asthma, and an intensive review of his past medical history did not reveal any wheezing episodes or recurrent bronchitis. Skin prick testing to 23 aeroallergens was negative; his spirometry demonstrated normal forced expiratory volume in 1 second (FEV_1) percent predicted (97%, normal above 79%) and FEV_1 to forced vital capacity ratio (FVC) (0.81, normal above 0.79). His symptoms of dyspnea (8/10 shortness of breath) were reproduced during a bike exercise test (after 7.5 minutes of exercise) with real-time laryngoscopy but without any significant drop in FEV_1, hyperventilation, or vocal cord adduction. He was evaluated by behavioral health and did not have significant anxiety or depression.

On plethysmography, he exhibited moderately increased hyperinflation (149%, moderate hyperinflation at or above 140% predicted)[5] with a normal residual volume to total lung capacity ratio (RV/TLC) at 24 (normal <30).[6] IOS has been shown to be a sensitive indicator of peripheral airway (<2 mm) obstruction through measurement of resistance at 5 Hz − 20 Hz (R5-R20).[7] It is estimated that approximately 75% of the small airways need to be obstructed before these changes can be detected by conventional spirometry parameters (FEV_1 and FEV_1/FVC).[8] This patient demonstrated increased percent peripheral airway resistance (R5-R20/R5) at 44% of total airway resistance (normal <30%)[8] and significant reversibility of small airway reactance measured by the area under the curve from R5 to resonant frequency (AX) at a 56% decrease from baseline (normal <40%).[8] He was discharged on fluticasone 44 two puffs twice daily and albuterol 2 puffs before exercise with the proper spacer technique. He was encouraged to slowly increase his exercise regimen.

At a follow-up 3 months after discharge, he reported marked improvement in shortness of breath and was able to exercise vigorously. He attributed his improvement to improved physical conditioning, diet changes to mitigate his reflux symptoms (such as not eating before bed), and optimal adherence to his inhaled fluticasone regimen. Follow-up IOS demonstrated decreased R5-R20/R5 (to 12.5% of total lung resistance) although his AX response to albuterol continued to be significantly elevated (51% decrease from baseline). The combination of elevated lung volumes and increased percent peripheral airway resistance that improved significantly with albuterol, but without obvious airflow limitation or reversibility as measured by FEV_1, suggested predominantly small airway obstruction and airway hyperinflation contributing to his dyspnea and exercise intolerance.

Approximately 50 children with post-COVID dyspnea have so far been evaluated in our program at National Jewish Health with the majority demonstrating either increased RV and/or RV/TLC, high R5-R20/R5, or AX reversibility to albuterol. Most children do not demonstrate low FEV_1 percent predicted or significant FEV_1 reversibility after albuterol, although FEV_1 reactivity to methacholine is sometimes present. Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) summarizes demographic characteristics, month of COVID diagnosis, and pulmonary function tests (PFTs) in 15 children with post-COVID dyspnea seen consecutively. Similar demographic characteristics were reported in the remaining post-COVID children whom we have assessed. Subsequent patients reported later acute COVID diagnoses suggesting that similar respiratory symptoms can occur after infection with newer COVID variants. All children reported in Table E1 were unvaccinated to COVID at the time of infection, and many, but not all, of the subsequent patients were unvaccinated. The

majority of patients did not report a previous diagnosis of asthma or previous treatment with asthma medications. Those with a history of previous asthma had nonpersistent asthma before COVID and were not taking daily inhaled corticosteroids except for 1 patient reported in Table E1.

Table E1 highlights the high frequency of elevated small airway resistance that improves with albuterol and/or lung hyperinflation in these patients. Almost all children with these abnormal PFTs report at least partial improvement of their dyspnea and improved exercise intolerance on initiation of inhaled corticosteroid therapy with, or without, long-acting β_2-agonist. In the cases with longitudinal measurements, R5-R20/R5 levels have also decreased, although they do not become normal in all cases, which suggests potential long-term airway changes. Further decreases in symptoms are seen over the next few months as children continue their medication treatment and exercise regimens. Although some of the symptomatic improvements were likely due to the natural course of the disease, the initiation of inhaler treatment and exercise regimen contributed to the accelerated trajectory of improvement after discharge.

In conclusion, we recommend that physicians who encounter children with post-COVID dyspnea and exercise intolerance assess the potential contribution of small airway reversible obstruction and lung hyperinflation in addition to other contributors such as anxiety, dysautonomia, and vocal cord dysfunction. A sustained trial of asthma controller medications and slowly increasing exercise intensity should be initiated in those who demonstrate these objective findings on IOS and/or plethysmography as spirometry is often normal in these patients.

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TABLE E1. Demographics and pulmonary function tests in post-COVID children with dyspnea

Age (y)	Sex/race/ethnicity	COVID vaccine before infection	Previous asthma	FEV_1 % predicted	FEV_1/FVC	% BD FEV_1	Methacholine FEV_1 PC20 (mg/mL)	% BD AX change	% Predicted RV	RV/TLC	Percent peripheral airway resistance ((R5-R20)/R5)
13	Female/White	No	No	82	78 ↓	−1	NP	63 ↑	151 ↑	31 ↑	36 ↑
5	Male/White	No	No	90	99	3	0.0625 ↓	25	238 ↑	46 ↑	38 ↑
16	Male/White	No	No	143	92	0	16	23	212 ↑	30 ↑	29
17	Female/White	No	No	99	90	0	1.3 ↓	50 ↑	247 ↑	35 ↑	14
14	Male/White/Hispanic	No	Yes	128	84	4	16	43 ↑	115	18	33 ↑
13	Male/White	No	No	81	91	2	16	58 ↑	132	31 ↑	39 ↑
17	Female/White/Hispanic	No	No	99	82	2	0.88 ↓	52 ↑	141 ↑	20	34 ↑
14	Female/White	No	No	108	76 ↓	1	3.32 ↓	32 ↑	159 ↑	26	13
14	Male/White	No	Yes	67 ↓	66 ↓	−31	NP	87 ↑	130	32 ↑	30 ↑
17	Female/White	No	Yes	99	87	5	16	NP	141 ↑	26	73 ↑
16	Male/White	No	Yes	75 ↓	75 ↓	8	NP	41 ↑	130	26	35 ↑
13	Female/White	No	Yes	77 ↓	82	9	NP	40 ↑	181 ↑	37 ↑	51 ↑
16	Female/White	No	Yes	87	95	4	11.57	19	153 ↑	34 ↑	35 ↑
16	Female/White	No	No	91	96	−2	4.93 ↓	13	145 ↑	28	4
12	Male/White	No	Yes	120	84	2	1.47 ↓	NP	110	19	5

The arrows indicate values above ↑ and below ↓ the normal range.

% BD AX, Area under the curve from R5 to resonant frequency reversibility after bronchodilator (albuterol) administration (normal <29.1%); *% BD FEV_1*, percent predicted forced expiratory volume in 1 second reversibility after bronchodilator (albuterol) administration (normal <12%); *% Predicted RV*, percent predicted residual volume (normal to mild hyperinflation <140%); *COVID*, coronavirus disease 2019; *FEV_1 % predicted*, percent predicted forced expiratory volume in 1 second (normal at or above 80); *FEV_1/FVC*, forced expiratory volume in 1 second divided by forced vital capacity (normal at or above 80); *Methacholine FEV_1 PC20*, methacholine dose when FEV_1 drops 20% from placebo dose (normal <16/mg/mL); *NP*, not performed; *RV/TLC*, residual volume divided by total lung capacity (normal <30); *R5-R20/R5*, percent resistance at 5 Hz − resistance at 20 Hz (normal <30).