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Protracted respiratory findings in children post-SARS-CoV-2 infection

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Abstract

Introduction: Although prolonged respiratory symptoms following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been described in adults, data are emerging that children also experience long-term sequelae of coronavirus disease 2019 (COVID-19). The respiratory sequelae of COVID-19 in children remain poorly characterized. In this study we describe health data and respiratory findings in pediatric patients presenting with persistent respiratory symptoms following COVID-19.

Methods: This study included patients referred to Pulmonary Clinic at the Children's Hospital of Philadelphia between December 2020 and April 2021 ($n = 29$). Inclusion criteria included a history of SARS-CoV-2 RNA positivity or confirmed close household contact and suggestive symptoms. A retrospective chart review was performed and demographic, clinical, imaging, and functional test data were collected.

Results: The mean age at presentation to clinic was 13.1 years (range: 4–19 years). Patients had persistent respiratory symptoms ranging from 1.3 to 6.7 months postacute infection. Persistent dyspnea and/or exertional dyspnea were present in nearly all (96.6%) patients at the time of clinic presentation. Other reported chronic symptoms included cough (51.7%) and exercise intolerance (48.3%). Fatigue was reported in 13.8% of subjects. Many subjects were overweight or obese (62.1%) and 11 subjects (37.9%) had a prior history of asthma. Spirometry and plethysmography were normal in most patients. The six-minute walk test (6MWT) revealed exercise intolerance and significant tachycardia in two-thirds of the nine children tested.

Conclusion: Exertional dyspnea, cough and exercise intolerance were the most common respiratory symptoms in children with postacute COVID-19 respiratory symptoms seen in an outpatient pulmonary clinic. Spirometry (and plethysmography when available), however, was mostly normal, and exertional intolerance was frequently demonstrated using the 6MWT.

KEYWORDS

breathlessness, exercise, functional capacity, postcovid syndrome, pulmonary function

1 | INTRODUCTION

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began spreading through the United States in early 2020, and there have been over 40 million cases in the United States as of September 2021, of which 4.8 million have been reported in children (14.8% of all cases). An overall rate of 6374 cases of SARS-CoV-2 infection per 100,000 children has been reported in the population.[1,2] Although severe illness due to SARS-CoV-2 infection is rare among children,[3] there is emerging data that children can also experience persistent symptoms known as post-acute COVID-19 syndrome.[4] Although the definition is evolving, most studies define long COVID as the persistence of symptoms or development of sequelae beyond 3 or 4 weeks from the onset of acute symptoms of COVID-19.[4] Evidence on long term outcomes in children is still limited to small studies with a range of prevalence. A recent cross sectional study out of Italy of 129 children found that 42.6% had at least one persistent symptom more than 60 days after infection, including children with history of asymptomatic or mild acute COVID-19, and 27.1% had at least one symptom 120 days or more after diagnosis.[5] Another study from Australia suggested that in children aged 0–19 years (median 3 years) with a history of predominantly mild COVID-19, 8% had persistent symptoms after 3–6 months.[6] A study from Switzerland comparing children who tested positive for SARS-CoV-2 to a population-based seronegative control group found a prevalence of 4% with persistent symptoms beyond 12 weeks.[7] In adult studies, persistent symptoms have been described in 76% of patients 6 months after diagnosis.[8] Previous studies have reported that even among young adults aged 18–34 years with no chronic medical conditions, approximately one in five had not returned to their usual state of health 14–21 days after acute infection.[9] Adult studies have described pulmonary manifestations of long COVID ranging from dyspnea to pulmonary fibrosis among COVID-19 survivors. Dyspnea is the most commonly reported persistent symptom in adult patients with a prevalence of 42%–66% at follow-up after 60–100 days. On pulmonary function testing, a reduction in diffusion capacity is the most frequently reported impairment, and the degree of reduction is directly related to the severity of acute illness.[4]

The respiratory sequelae of COVID-19 in pediatric patients, however, remain poorly characterized. The aim of this study was to describe baseline health data and respiratory findings in a cohort of pediatric patients experiencing prolonged symptoms following acute COVID-19 infection.

2 | METHODS

Subjects were referred to Pulmonary Clinic at the Children's Hospital of Philadelphia (CHOP) for evaluation of persistent respiratory symptoms 6 weeks or more after acute SARS-CoV-2 infection between December 2020 and April 2021. Inclusion criteria included a history of SARS-CoV-2 RNA positivity or confirmed close household contact and suggestive clinical symptoms. Demographic, clinical, imaging, and functional test data were collected through retrospective chart review. All patients had spirometry data available except for one patient who was too young to cooperate. Patients underwent plethysmography, diffusion studies, and six-minute walk tests (6MWT) at the discretion of the clinician. All testing was performed in compliance with current ATS guidelines and all testing was performed in a negative pressure room in which the Pulmonary Function Testing Therapist used infection control practices in accordance with institutional policy. Spirometry was performed using a Morgan Scientific SpiroAir rolling seal spirometer (Morgan Scientific). Plethysmography was performed using a Morgan Scientific plethysmograph (Morgan Scientific). DLCO testing was performed using the Morgan Scientific SpiroAir (Morgan Scientific). PFT data were normalized for age, gender, race, and height. Pulmonary function and 6MWT variables were referenced to predicted normal values.[10–12] Lower limit of normal was defined as Z scores below 1.64. Obstructive ventilatory defects were defined as a ratio of forced expiratory volume in 1 second to forced vital capacity forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) less than 80% predicted. Bronchodilator response was considered significant if FEV_1 improved by more than 12% and/or FEF_{25-75} improved by more than 25%. FVC and TLC were considered normal if above 80% predicted and considered restrictive if below 80% predicted. RV below 130% predicted and RV/TLC below 30% were considered normal. DLCO of 75%–100% predicted was considered normal. The study was approved by the CHOP Institutional Review Board for exempt research (IRB# 21-018473).

3 | RESULTS

3.1 | Study population

Over a 5-month period, 29 pediatric subjects presented to CHOP Pulmonary Clinic for evaluation of persistent symptoms 6 weeks or more after SARS-CoV-2 infection (Table 1). Of subjects seen for COVID-related complaints, 14% had previously been followed in CHOP Pulmonary Clinic for other concerns before their acute SARS-CoV-2 infection. The mean age at presentation was 13.1 ± 3.9 years (range: 4–19 years). Females (58.6%) and non-whites (55.2%) made up the majority of the patients seen. Many subjects were either overweight (24.1%; body mass index [BMI] between 85th and 95th percentile) or obese (37.9%; BMI >95th percentile). Baseline atopy, defined as presence of asthma, eczema, and/or allergic rhinitis, was present in 65.5% of subjects. Of the eleven subjects with asthma, 55% had mild asthma, 36% had moderate asthma, and 9% had severe asthma. Eight subjects with asthma were previously prescribed a daily inhaled corticosteroid. Most subjects (96.4%) reported engagement in regular physical activity before acute COVID-19.

3.2 | Acute COVID illness characteristics

All subjects had positive SARS-CoV-2 PCR testing or confirmed close household contacts with positive SARS-CoV-2 testing and suggestive clinical symptoms at the time of initial illness. The most common reported acute COVID-19 symptoms were fever (69%), cough (55.2%), dyspnea (48.3%), ageusia/anosmia (41.4%) and myalgia (37.9%) (Table 2). Only

TABLE 1 Study population

Mean ± *SD* [range]	Entire population (*n* = 29)
Age (years)	13.1 ± 3.9
	[4, 19]
Sex (% female)	58.6%
Race (% non-white)	55.2%
Ethnicity (% Hispanic)	13.8%
Reported baseline stamina (% reduced)	3.6%
	(*n* = 28)
Baseline respiratory support (% yes)	0.0%
	(*n* = 28)
Baseline asthma (% yes)	
Mild intermittent	10.3%
Mild persistent	10.3%
Moderate persistent	13.8%
Severe persistent	3.4%
Any asthma	37.9%
Baseline atopy (% asthma, eczema, and/or allergic rhinitis)	65.5%
Any history of smoking or vaping (% yes)	0.0%
Secondhand exposure to smoking or vaping (% yes)	3.4%
Overweight/obesity (% yes)	62.1%

TABLE 2 Acute COVID-19 characteristics

Mean ± *SD* [range]	Entire population (*n* = 29)
Symptomatic at time of testing (% yes)	93.1%
Symptoms during illness (% yes)	
Fever	69.0%
Cough	55.2%
Dyspnea	48.3%
Ageusia/anosmia	41.4%
Myalgia	37.9%
Chest radiograph opacities (% yes)	23.0%
	(*n* = 13)
Hospitalization (% yes)	
Acute phase	13.8%
Delayed (MIS-C)	3.4%
Duration of acute illness (days)	13.4 ± 11.0
	[2, 49]

four patients (13.8%) required hospitalization during initial illness. All four were treated with systemic steroids and one received remdesivir. No patient required intubation. One additional patient was hospitalized 6 weeks after acute symptom onset owing to multisystem inflammatory syndrome in children (MIS-C). Chest radiograph opacities were present in 3 of 13 patients (23%) who had imaging performed at the time of acute illness.

3.3 | Post-COVID characteristics

Subjects presented to clinic a mean of 3.2 ± 1.5 months after a SARS-CoV-2 positive PCR or confirmed close contact and suggestive clinical symptoms (range: 1.3–6.7 months) (Table 3). Persistent dyspnea and/or exertional dyspnea were present in nearly all (96.6%) of the patients at the time of clinic presentation. Other commonly reported chronic symptoms were cough (51.7%) and exercise intolerance (48.3%). Fatigue was reported in four subjects (13.8%). One subject had an ongoing supplemental oxygen requirement. Oxyhemoglobin saturations ranged from 97% to 100%. Lung auscultation findings were normal in 27 subjects. Two subjects (6.9%) had abnormal auscultatory findings including decreased breath sounds and intermittent wheezing. Spirometry was performed in 28 patients. Mean percent predicted spirometry results included an FEV_1 of 107 ± 12%, an FVC of 110 ± 16%, an FEV_1/FVC of 86 ± 8%, and an $FEF_{25\%-75\%}$ of 100 ± 23%. Obstructive ventilatory defects were present in three subjects. There were no patients with restrictive ventilatory defects. Improvement following bronchodilator administration was observed in 38.1% of the 21 subjects who underwent post-bronchodilator testing. Broncho-responsiveness occurred in eight patients, four of whom had known underlying asthma and four of whom did not. Plethysmography was performed in 14 subjects and diffusion capacity testing was performed in 15 subjects. Average percent predicted plethysmography results include a TLC of 108 ± 17%, a VC of 120 ± 14%, an FRC of 99 ± 20%, and a RV of 81 ± 48%. An elevated RV/TLC above 30% was observed in four patients ranging from 32% to 89%, suggestive of air trapping. Average percent predicted DLCO was 95 ± 17% and DLCO/VA was 96 ± 14%. Exercise intolerance on a 6MWT was observed in six out of nine patients (66.7%). Notably, these patients were found to have significant tachycardia for age (HR range: 120–213 bpm). Of the eight patients who had chest radiographs performed at the time of follow-up, only one was abnormal (12.5%). All of the 15 patients who had follow-up cardiac evaluations had normal EKG and/or echocardiographic findings (Table 3).

4 | DISCUSSION

This is a descriptive study of patients referred to a tertiary care pediatric pulmonary clinic for chronic respiratory symptoms 1–7 months after a diagnosis of SARS-CoV-2 infection. Most patients seen for protracted respiratory symptoms following SARS-CoV-2

TABLE 3 Post-COVID-19 characteristics

Mean ± *SD* [range]	Entire population (*n* = 29)	
Duration of persistent symptoms at time of presentation (months)	3.2 ± 1.5	
	[1.3, 6.7]	
Symptoms at presentation (% yes)		
Cough	51.7%	
Dyspnea and/or exertional dyspnea	96.6%	
Exercise intolerance	48.3%	
Fatigue	13.8%	
Oxygen requirement	3.4%	
Lung auscultation (% abnormal)	6.9%	
Pulse oximetry (% saturation)	99 ± 1%	
	[97%, 100%]	
Spirometry (*n* = 28 tested, except where noted)		
FVC (% predicted; *Z* score)	110 ± 16%	0.79 ± 1.31
	[79%, 150%]	[−1.82, 4.16]
FEV_1 (% predicted; *Z* score)	107 ± 12%	0.57 ± 0.97
	[79%, 130%]	[−1.76, 2.64]
FEV1/FVC (% predicted; *Z* score)	86 ± 8%	−0.26 ± 1.23
	[62%, 100%]	[−3.39, 2.31]
$FEF_{25\%-75\%}$ (% predicted; *Z* score)	100 ± 23%	−0.03 ± 1.03
	[47%, 145%]	[−2.52, 1.99]
Bronchodilator response (% yes; *n* = 21)	38.1%	
Plethysmography (*n* = 14 tested, except where noted)		
TLC (% predicted; *Z* score)	108 ± 17%	0.62 ± 1.46
	[78%, 136%]	[−1.86, 2.99]
VC (% predicted; *Z* score)	120 ± 14%	0.94 ± 0.63
	[93%, 148%]	[−0.34, 2.12]
FRC (% predicted; *Z* score)	99 ± 20%	−0.05 ± 1.28
	[66%, 136%]	[−2.01, 2.14]
RV (% predicted; *Z* score; *n* = 13)	81 ± 48%	−0.67 ± 1.73
	[9%, 202%]	[−3.27, 3.63]
RV/TLC (% predicted; *Z* score)	28 ± 20%	−0.16 ± 0.19
	[8%, 89%]	[−0.47, 0.21]
Diffusion studies (*n* = 15 tested)		
DLCO (% predicted; *Z* score)	95 ± 17%	−0.40 ± 1.14
	[70%, 133%]	[−2.40, 2.16]
DLCO/VA (% predicted; *Z* score)	96 ± 14%	−0.29 ± 0.94
	[69%, 125%]	[−2.19, 1.53]
Respiratory muscle strength (*n* = 7 tested)		
Mean inspiratory pressure (% predicted)	87 ± 16%	
	[58%, 106%]	
Mean expiratory pressure (% predicted)	75 ± 17%	
	[50%, 96%]	
6 min walk test (% impaired; *n* = 9 tested)	66.7%	
Chest radiograph (% abnormal; *n* = 8 tested)	12.5%	

Abbreviations: FEV1, forced expiratory volume in 1 second; FEV, forced vital capacity.

infection were not hospitalized and had mild acute-COVID-19 symptomatology. Protracted respiratory symptoms post-COVID-19 occurred in children as young as 4 years old.

In our study, patients reported persistent exertional dyspnea, cough and exercise intolerance, however, spirometry, plethysmography, and diffusion studies were primarily normal in those children who underwent pulmonary function testing as were pulse-oximetry and imaging. The 6MWT, however, revealed exercise intolerance and significant tachycardia in two-thirds of the nine children who were tested. This finding suggests that the 6MWT may be a low-cost and simple way to evaluate children after COVID-19 and provide a quantitative result that can be trended over time to assess improvement or progression of disability.

The most frequent protracted symptoms reported by our patients included dyspnea and exertional dyspnea, exercise intolerance and cough. This differs from existing studies of children with long COVID in which the most frequently reported symptoms among seropositive children include fatigue, increased need for sleep, insomnia, mild postviral cough, nasal congestion, muscle and joint pains, and difficulty concentrating.[5–7] Our findings were similar to one of the first case reports of children with long-term effects after COVID-19 featuring five children, all of whom experienced dyspnea and three of whom experienced low exercise tolerance.[13] In comparable studies of adults who did not require hospitalization during acute COVID-19, the most common complaints were dyspnea and fatigue.[14,15] In contrast, in our pediatric study population, fatigue was only reported by four patients (13.8%). Similar to our study in which we found that exertional dyspnea was presented in almost all patients, Townsend et al.[16] reported that 62% of adult survivors of COVID-19 reported persistent dyspnea and exertional limitation 75 days after their acute illness. Interestingly, persistent dyspnea and exertional limitation were not associated with initial disease severity in their study.

We found an increased prevalence of atopy and obesity in our study population that presented with prolonged post-SARS-CoV-2 infection respiratory symptoms. According to the CDC, the most

recent national asthma data from 2019 suggests an asthma prevalence of 7% in children under 18 years.[17] The asthma prevalence in our study population was 37.9%, which is nearly five times higher than the general population, and two-thirds were atopic. This may suggest that asthma and atopy are risk factors for developing long COVID respiratory symptoms in children and will require larger studies to confirm this association. Obesity, defined as a BMI above the 95th percentile, may also be linked to persistent symptoms after COVID-19. Our study population has a higher rate of child obesity of 37.9% compared to the local population rate of 20.3%[18]; however, this again may reflect study sample bias. These findings echo those in a recent prospective cohort study out of Russia evaluating risk factors for long COVID in previously hospitalized children, which found that predictors of persistent symptoms included older age (6–18 years as compared to under 2 years) and history of allergic disease. Among children 6 years and older, being overweight or obese and severe COVID-19 were associated with persistent symptoms, although the authors report wide confidence intervals and the need for larger studies to confirm findings.[19]

More studies are needed regarding effective management of patients with post-COVID syndrome. Existing guidelines and rehabilitation programs are primarily directed at adult survivors of COVID-19 and recommend multidisciplinary treatment approaches including pulmonary rehabilitation and physical therapy.[20] There are limited studies that report improvement in persistent symptoms following vaccination,[21] but so far there are no studies looking at the impact of vaccination in pediatric patients. Pacing and gradual return to exercise may lessen exertional symptoms.[20] Additionally, the high prevalence of asthma and improvement following bronchodilator administration observed in 38.1% of patients suggests that there may be a role for bronchodilators and inhaled corticosteroids in some pediatric patients.

Our study had several limitations. First, our population was recruited as a convenience sample. Patients in this study were seen in a pediatric pulmonary clinic and thus may be more motivated to seek out specialty care or have fewer barriers to accessing care. It is likely that our sample represents a small fraction of total cases of protracted COVID-19 symptoms in children within our catchment area, with the majority of cases being seen by primary care physicians. The youngest subject in our population was 4 years old, which may reflect the youngest age for subjects to actively report symptoms, thus we cannot comment on whether these protracted symptoms could be observed in even younger patients. We were not able to make any conclusions about the prevalence of long COVID in children with acute COVID illness or if severity of acute COVID illness correlates with prevalence and symptom severity of long COVID in children due to our limited sample size. Future studies should include population-based studies with larger sample sizes to determine the frequency of long-term complications of COVID-19 in children. The relationship between initial SARS-CoV-2 infection severity and long COVID in children, as well as identification of other risk factors, represents an important future area of study.

A final major limitation of our study is that we did not have complete data on the patients. Additionally, although the same clinical data was collected by the physicians seeing these patients, a standardized questionnaire was not used, and as such one patient is missing baseline stamina and respiratory support information. This highlights the importance of increased objective testing and surveillance for respiratory sequelae in children post-COVID-19. Children in our study also did not undergo third level tests which may have revealed evidence of pulmonary damage as an explanation for persistent respiratory symptoms. In a case report by Buonsenso et al.,[22] they performed cardiopulmonary exercise testing and lung SPECT/CT in an adolescent with ongoing symptoms 7 months after diagnosis, which revealed evidence of pulmonary circulation dysfunction and possible lung microvascular or endothelial damage. The adolescent in the case report presented with similar findings to our patients including poor exercise tolerance, tachycardia and easy fatigability on 6MWT, and normal lung flows and volumes. Elevated plasmablasts and proinflammatory cytokines found in the adolescent support the proposed pathological mechanism of long COVID as resulting from immune dysregulation with a persistent hyperinflammatory state resulting in endothelial damage and microvascular injury.[4,22,23]

The burden of caring for COVID-19 survivors is expected to be tremendous, and future medical and social interventions must consider the late sequelae of SARS-CoV-2 infection. Even though children in general experience less severe COVID-19 symptomatology than adults, our study demonstrated that children can have significant long-term respiratory symptoms which can impact quality of life in these children. Our study indicates that ongoing respiratory morbidity can persist even in children with mild acute SARS-CoV-2 infection history and when impairments are not clearly identified by available objective testing. Since children are increasingly becoming sick with the delta variant, more research is urgently needed into the prevalence and prognosis of postacute COVID symptoms in children as well as the risk factors for prolonged COVID-19 to guide targeted intervention and inform management. The existing case reports about lung perfusion defects also point to a need for further investigation into chronic organ damage in seropositive children. There will be an increasing need to follow these children longitudinally to determine the long-term consequences of SARS-CoV-2 infection on respiratory health, as this information will have important implications for public health surveillance, health resource allocation, clinical research, and future treatments.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization: all authors; *design*: all authors; *data collection*: Shoshana C. Leftin Dobkin; *data analysis*: Shoshana C. Leftin Dobkin

and Joseph M. Collaco; *data interpretation*: Shoshana C. Leftin Dobkin, Joseph M. Collaco, and Sharon A. McGrath-Morrow; *manuscript writing*: Shoshana C. Leftin Dobkin; *manuscript review*: all authors. Shoshana C. Leftin Dobkin had full access to the study data and takes responsibility for the integrity of the data and the accuracy of the analysis.

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