for frontline providers. While our data is limited, this article provides preliminary information for future studies of antibody treatment for a disease that carries a significant morbidity in the pediatric population.

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LONG COVID IN CHILDREN

Observations From A Designated Pediatric Clinic

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Abstract: Systematic data are lacking on pediatric long COVID. This study prospectively assessed 90 children with persistent symptoms who presented to a designated multidisciplinary clinic for long COVID. In nearly 60%, symptoms were associated with functional impairment at 1–7 months after the onset of infection. A comprehensive structured evaluation revealed mild abnormal findings in approximately half the patients, mainly in the respiratory aspect.

Key Words: bronchodilator, lung function, postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection, respiratory

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Long-term follow-up of adults diagnosed with acute coronavirus disease 2019 (COVID-19) has shown that a substantial proportion experience persisting symptoms months after the initial diagnosis.[1,2] To date, systematic data are lacking on long COVID or postacute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children.[3] We prospectively analyzed persistent symptoms in children who recovered from COVID-19, and described the diagnostic yield of a comprehensive clinical evaluation.

METHODS

This study prospectively assessed children ≤18 years of age who presented to a designated multidisciplinary clinic for long COVID, at a tertiary pediatric center, from November 2020 to April 2021, following referral by their general practitioner. SARS-CoV-2 infection was microbiologically confirmed by real-time quantitative reverse transcription polymerase chain reaction during acute infection or by subsequent serology using an in-house enzyme-linked immunosorbent assay (The Central Virology Laboratory of the Ministry of Health at Sheba Medical Center, Tel Hashomer) until mid-March and Abbot ARCHITECT SARS-CoV-2 IgG Immunoassay, thereafter. All the patients underwent a structured evaluation >4 weeks from diagnosis. This included assessment of symptoms and their impact on daily activities by means of a structured interview conducted by a senior pediatrician with >10 years' experience; a physical examination, blood tests, electrocardiograph and a chest radiograph. In the event of cardiorespiratory symptoms, a pulmonary function test (for children older than 6 years) and echocardiography were performed. Further testing, such as bronchodilator response testing and cardiac magnetic resonance imaging (MRI), was done following abnormal findings on the initial evaluation. Additionally, data on background illnesses and on acute COVID-19 disease were retrieved from patients' electronic files. Severity of the acute COVID-19 disease was classified according to the National Institute of Health symptom severity criteria.[4]

Persistent symptoms were stratified by age (≤11 versus >11 years) and compared by χ^2 (IBM SPSS Statistics, Version 22.0). Written informed consent was obtained from parent or legal guardian; the study was approved by the institutional review board (RMC-20-0885).

RESULTS

Ninety children, mean age 12 ± 5 years, were assessed at a median of 112 days (range: 33–410) after COVID-19 diagnosis. One adolescent who tested positive for COVID-19 was excluded from the analysis because during the initial evaluation, diabetic ketoacidosis was diagnosed; following medical care, his symptoms of fatigue and weight loss resolved. The cohort comprised mainly previously healthy children who exhibited a mild symptomatic acute disease (Table 1). The sex ratio showed a minor male predominance. Twenty-five percent were overweight, with a body mass index >85th percentile for age, in accordance with national published rates.[5] The most common reason for patient referral was dyspnea (30, 33.3%), followed by myalgia (12, 13.3%) and headache (8, 8.8%).

The median number of reported symptoms was 4 (range: 1–14). Fatigue (64, 71.1%), dyspnea (45, 50.0%) and myalgia (41, 45.6%) were the most frequently reported symptoms, and were significantly associated with older age >11 years (Table 1, Supplemental Digital Content 1, http://links.lww.com/INF/E492). Additional persistent symptoms included sleep disturbances (30, 33.3%), chest pain (28, 31.1%), paresthesia (26, 28.9%), headache (26, 28.9%), hair loss (24, 26.7%), anosmia-ageusia or parosmia/euosmia (23,25.6%), gastrointestinal symptoms (18, 20.0%), dizziness (17, 18.9%), weight loss of >5% of body weight (17, 18.9%), memory impairment (16, 17.8%), vasomotor complaints

TABLE 1. Demographic and Clinical Characteristics of 90 Children with Long COVID, and the Main Features of the Medical Evaluation

General Characteristics	N (%)
Age, mean ± SD, yrs	12 ± 5
Gender, male:female	1.4:1
BMI percentile by WHO growth charts > 85	23 (25.6)
Very early preterm birth <32 wks gestation	2 (2.2)
Early preterm birth 32–36 wks gestation	3 (3.3)
Background medical conditions	
Immunodeficiency*	5 (5.6)
Autoimmune or inflammatory disease†	4 (4.5)
Asthma	2 (2.2)
Anxiety or depressive disorder	3 (3.3)
Attention deficit hyperactivity disorder	12 (13.3)
Other‡	33.3
Participation in competitive sports	12 (13.3)
Severity of the acute COVID-19 illness§: asymptomatic	3 (3.3)
Mild	82 (91.1)
Moderate	6 (6.7)
Severe	2 (2.2)
Hospitalization during the acute illness	11 (12.2)
Positive COVID-19 qRT-PCR during the acute illness, n = 89	89 (100)
COVID-19 serology during evaluation,¶ n = 72, positive	58 (80.6)
Borderline	5 (5.6)
PIMS before evaluation	1 (1.1)
Medical evaluation	
Positive findings on physical examination	5 (5.6)‖
Laboratory investigation**	
Sedimentation rate > 20 mm/h or C-reactive protein > 0.5 mg/dL	4 (4.9)
Troponin≥ 14 ng/L	1 (1.3)
Creatine phosphokinase ≥ 200 units/L	11 (14.1)
Ferritin ≤ 20 µg/L	29 (43.9)
Hemoglobin ≤ 11 g/dL	3 (3.6)
Pulmonary evaluation	
Chest radiograph changes	12 (133)††
Pulmonary function tests	
Abnormal spirometry, FEV1 < 80% or FEV1/FVC < 0.8, n = 60	5 (8.3)
Abnormal exercise challenge test,‡‡ ΔFEV1 ≥ 12%, n = 51	3 (5.9)
Positive bronchodilator response, ΔFEV1 ≥ 12%, n = 29	15 (51.7)
Air trapping by plethysmography, RV/TLC > 125%, n = 55	15 (27.3)
Diffusion capacity < 70%, n = 50	1 (2.0)§§
Cardiac evaluation	
Abnormal findings on electrocardiograph	2 (2.2)¶¶
Abnormal findings on echocardiography, n = 63	0 (0)
Abnormal holter, n = 4	0 (0)
Abnormal cardiac MRI, n = 3	1 (33.3)
Maximal pulse during exercise stress test <180 b/min,[6] n = 51	34 (66.7)

BMI, body mass index; FEV1, forced expiratory volume in the first second; FEV1/FVC, ratio of FEV1 to forced vital capacity; PIMS, pediatric inflammatory multisystem syndrome; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RV/TLC, ratio of residual volume to total lung capacity; WHO, World Health Organization.

*Including, kidney transplantation due to microscopic polyangiitis (1), kidney transplantation due to Schimke immuno-osseous dysplasia (1), glioma with chemotherapy (1), s/p bone marrow transplantation due to myelodysplastic syndrome (1), asplenia due to spherocytosis (1).

†Including, Crohn's disease (1), Familial Mediterranean Fever (1), type 1 diabetes (1), celiac disease (1).

‡Including, dysplastic kidney (1), bilateral cochlear implant (1), convulsive disorder (1).

§By the National Institute of Health symptom severity criteria.[4]

¶In 4 adolescents, serology was taken after 1 dose of BNT162b2 (Pfizer-BioNTech COVID-19 vaccine).

‖Including, decreased muscle strength, dyspnea or tremor.

**Serum was depleted in 17 children; One patient refused blood tests.

††Including infiltrates (7), peribronchial thickening (3) and interstitial pattern (1).

‡‡The exercise test was terminated prematurely in four patients due to dyspnea or myalgia.

§§S/p severe acute COVID-19.

¶¶Inverted T waves and ST segment elevation.

(13, 14.4%), arthralgia (13, 14.4%), tremor (12, 13.3%), cough (9, 10.0%), palpitations (8, 8.9%), difficulty in concentration (8, 8.9%), tic exacerbation (2, 2.2%) and tinnitus (1, 1.1%). Uncommon symptoms in young children included recurrent febrile episodes (2, 2.2%), developmental regression (2, 2.2%) and obstructive sleep apnea (2, 2.2%). These were temporally associated with COVID-19 infection, had no alternative explanation despite a comprehensive evaluation and resolved after about 10–12 weeks. Fifty-three children (58.9%) reported impairment in daily activities due to symptoms.

The comprehensive medical evaluation revealed abnormal findings in a substantial number of patients, mainly in the

respiratory aspect. Twenty-seven (45.0%) of 60 patients who underwent pulmonary function tests due to cardiorespiratory symptoms had abnormal findings. These were compatible with a mild obstructive pattern, as evident by low values of forced expiratory volume in the first second on spirometry, and by air trapping on lung volume evaluation. Following bronchodilators in the patients with abnormal or borderline pulmonary function tests, more than half (15/29) exhibited reversibility of the obstructive defect (Table 1). Abnormal pulmonary function tests were not associated with a history of atopy (8/27 vs. 13/33, $P = 0.431$).

For all 51 patients who underwent an exercise stress test, the maximal pulse was lower than the age-specific mean; for 34 (66.7%), the value was below the minimal threshold value (−2 SDs),[6] suggesting some degree of chronotropic incompetence. Cardiac investigation was mostly normal; echocardiography showed normal left ventricular ejection fraction and the absence of pulmonary hypertension in all 63 patients. Abnormal findings on electrocardiograph were found in 2 adolescent patients who previously participated in competitive sports. One of them had transiently elevated troponin levels and mild lateral wall thickening on cardiac MRI. Significant laboratory findings were elevated levels of creatine phosphokinase and low ferritin levels (Table 1).

DISCUSSION

This prospective cohort preliminary study provides a detailed description of the continuum of persisting symptoms in children with long COVID and the results of their medical investigation at a designated pediatric clinic. Despite a mild acute disease and lack of background illness in the vast majority, for nearly 60%, symptoms were associated with functional impairment at 1–7 months after the onset of infection. The 2 most common symptoms were fatigue and dyspnea, as has been described in adults.[1,2] However, obstructive sleep apnea and developmental regression were not previously described and warrant further research. Interestingly, several symptoms were more common among older children. In contrast to reports in adults in which females were at greater risk for long COVID,[7] our cohort showed a minor male predominance. Also, among adults, it was suggested that obesity is associated with a greater risk of long COVID;[8] this suggestion was not supported by the normal weight distribution of our cohort population.

Although radiologic and spirometric changes were mild, they were observed in more than half the patients. This supports the importance of pulmonary evaluation, and the potential for treatment with bronchodilators and inhaled corticosteroids. Another treatment approach may focus on dietary habits and may include ferritin in the laboratory workup. Conversely, none of the children exhibited abnormal findings on echocardiography, raising questions as to its necessity in children, in the presence of a normal electrocardiograph.

The study is limited by the small sample size and single-center design; however, it lays the groundwork for designing therapeutic interventions for long COVID in children. Also, a baseline pre-COVID evaluation of the patients is lacking. In addition, since the study was not population-based, the prevalence of long COVID could not be assessed. However, this was not the aim of the study, but rather to describe the range of symptoms and the diagnostic yield of the medical investigation.

In conclusion, this study confirms the morbidity associated with long COVID in children, and highlights the need for multidisciplinary pediatric clinics for evaluation and treatment.

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DELAYED BRONCHIOLITIS EPIDEMIC IN FRENCH PRIMARY CARE SETTING DRIVEN BY RESPIRATORY SYNCYTIAL VIRUS: PRELIMINARY DATA FROM THE OURSYN STUDY, MARCH 2021

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Abstract: We report early results from a prospective primary care bronchiolitis surveillance study in France in which a 10-week delayed epidemic was detected from February to March 2021. Among 225 children under 2 years with swab testing for a first bronchiolitis episode, 55% had a positive test for RSV, 0 for influenza, and 1 for severe acute respiratory syndrome coronavirus 2.

Key Words: respiratory syncytial virus, bronchiolitis, nonpharmaceutical intervention, COVID-19

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Data are available upon reasonable request.

R.C., C.L., M.B. and C.J. conceived the study. R.C., C.B., F.H., M.Z. and F.C.S. involved in data collection. R.C., C.L., M.B., A.R. and S.B. participated in data analysis and interpretation. R.C., C.L., M.B., A.R. and S.B. responsible in drafting the article. All authors involved in revising the article for important intellectual content and approved the final version submitted. R.C., C.L., M.B. and A.R. participated in study supervision.