

Long COVID in Children and Adolescents

A Retrospective Study in a Pediatric Cohort

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Abstract: Studies on long coronavirus disease (COVID) in children are scarce. We aimed to describe persistent symptoms and identify risk factors for its development. In our study population, 17.6% presented with long COVID, with respiratory symptoms more frequent in the first weeks and neuropsychiatric symptoms over time. Chronic conditions and obesity were risk factors, and adolescents were at a greater risk for long COVID.

Key Words: long COVID, fatigue, COVID-19

(*Pediatr Infect Dis J* 2023;42:e109–e111)

Children infected with Severe acute respiratory syndrome coronavirus 2 are usually asymptomatic or with a mild form of coronavirus disease (COVID).¹ While the acute symptoms are well defined, the long-term symptoms are not. Most COVID-19 patients achieve full recovery within 3–4 weeks after infection; however, in some cases, persistent symptoms can be seen weeks or months after recovery.² According to National Institute for Health and Care Excellence guidelines, symptoms from onset to 4 weeks after diagnosis are considered acute COVID-19.³ The persistence of symptoms from 4 to 12 weeks is defined as ongoing symptomatic COVID-19, whereas symptoms that continue 12 weeks after diagnosis are considered post-COVID-19. Either ongoing symptomatic COVID-19 or post-COVID-19 is considered long COVID.³ In children, information on COVID-19 persistent symptoms remains scarce. Recent studies have shown that common persistent symptoms include fatigue, headache, postviral cough, anosmia, dyspnea and chest pain.^{4–6} In this study, we aimed to identify the prevalence of COVID-19 persistent symptoms in patients presenting to a tertiary hospital and to investigate possible risk factors for the development of long-term COVID.

MATERIALS AND METHODS

Participants

This was an observational, analytic and retrospective study. Patients from 0 to 18 years old who had a positive Severe acute respiratory syndrome coronavirus 2 RT-PCR test when tested during an emergency department visit or during hospitalizations or before elective surgery between March 2020 and September 2021 were included. Regarding criteria for performing Severe acute respiratory syndrome coronavirus 2 test in the emergency department, national guidelines from the Directorate-General for Health were followed. Suspicious cases in which these tests were performed consisted in at least one of the following: cough, fever, respiratory distress, anosmia and/or dysgeusia. Furthermore, in children presenting with at least 2 other symptoms (nausea, vomiting, diarrhea or abdominal pain), or with a known epidemiologic link, decision for testing was decided case by case. Cases of children with multisystem inflammatory syndrome and diagnosed with bronchiolitis were excluded. They were monitored on a home-care basis by daily phone calls until fulfilling the criteria for discharge, and then with dedicated follow-up appointments at 4, 12 and 24 weeks.

Data Collection

For any patient diagnosed with COVID-19, the following data were collected: age, sex, pre-existing comorbidities (obesity, respiratory, renal, hemato-oncology, gastrointestinal, neurologic, metabolic, cardiac, chromosome abnormality, immunosuppression or autoimmune condition), symptoms on admission (fever, cough, rhinorrhea, respiratory distress, nasal congestion, sore throat, anosmia, dysgeusia, anorexia, vomiting, diarrhea, headache, myalgias, fatigue and rash), symptom duration, COVID's severity (mild, moderate or severe) and persistent symptoms (fever, persistent cough, respiratory distress, anosmia, rhinorrhea, dysgeusia, joint pain, vomiting, anorexia, diarrhea, headache, myalgia, fatigue, sleep disturbances, behavioral changes and concentration difficulties). Adolescents were defined as those above the age of 10 years. Fever was considered when temperature was >37.6 °C axillary, 37.8 °C tympanic or 38 °C rectal. Obesity was defined as a body mass index $> P99$ between 2 and 5 years and above $P97$ between 5 and 18 years. Anosmia and dysgeusia were systematically assessed in children >5 years of age. The severity of COVID-19 was defined as mild: presence of mild symptoms without respiratory distress, dyspnea or abnormal chest imaging; moderate: clinical or radiographic lower respiratory disease but with oxygen saturation $\geq 94\%$ on room air; and severe: oxygen saturation $<94\%$ on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mm Hg, and respiratory rate above normal or lung infiltrates $>50\%$.⁷ Data were extracted from the electronic medical records. The research protocol was approved by the Ethics Committee. All collected data were kept confidential.

Statistical Analysis

Statistical analysis was performed using the “Statistical Package for the Social Sciences.” Descriptive statistics are presented

Accepted for publication December 16, 2022

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The authors have no funding or conflicts of interest to disclose.

All relevant data are within the paper.

All authors have made substantial contributions to (1) the conception and design of the study, or the acquisition of data or analysis and interpretation of data, (2) drafting the article and revising it critically, (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to the data in the study and have approved the final version of the article, including the authorship list. The manuscript included related data and tables has not been previously published and the manuscript is not under consideration elsewhere.

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ISSN: 0891-3668/23/4204-e109

DOI: 10.1097/INF.00000000000003829

as means (M) and standard deviations for symmetrically distributed variables; medians (Mdn) and interquartile ranges (IQRs) are presented for nonsymmetrically distributed variables. Frequencies (n) and proportions (%) are presented as qualitative variables. Normality was assessed using histogram observation. T-tests were used to compare quantitative variables. Chi-square tests were used to compare proportions. Logistic regression was used to measure the association between the dependent variable and a set of independent variables. Odds ratios (ORs) and 95% confidence intervals were calculated. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 237 patients were included, 54.4% of whom were male. The mean age was 79 months, and 35.4% were adolescents. Pre-existing comorbidities were present in 36.7% of them, with respiratory and neurologic conditions being the most prevalent (13.5 vs. 9.7%, respectively). Among the respiratory conditions, recurrent wheezing was the most frequent, and among neurology conditions, epilepsy was the most frequent. Obesity was identified in 18 patients (7.6%).

The most common symptoms on admission were fever (60.3%), cough (42.2%) and rhinorrhea (34.6%). Thirty patients (12.7%) were asymptomatic, 80.2% had mild disease, 4.2% had moderate disease and 3.0% had severe disease, which implied ICU admission. Forty-nine (20.7%) patients required hospital admission, but only 18 (7.8%) of them were due to COVID. The main cause of admission among them was respiratory failure needing oxygen. The duration of hospitalization ranged from 1 to a maximum of 24 days (median, 6 days; IQR, 7 days).

Of the 237 patients, 144 (60.8%) were evaluated at 4 weeks, 136 (56.2%) at 12 weeks and 138 (57.0%) at 24 weeks (Table 1). Sixty-four (27.0%) patients had 3 follow-up appointments, while 75 (31.6%) had 2 of them. At 4 weeks, 28 (19.4%) patients reported symptoms, with fatigue being the most common ($n = 13$; 9.0%), followed by persistent cough ($n = 8$; 5.6%) and rhinorrhea ($n = 9$; 6.2%). At 12 weeks, 18 (13.3%) patients had symptoms, with fatigue being the most common ($n = 10$; 7.5%), followed by behavioral changes ($n = 6$; 4.5%) and sleep disturbances ($n = 5$; 3.7%). At 24 weeks, 9 (6.5%) still had symptoms, predominantly sleep disturbances ($n = 5$; 3.7%), fatigue ($n = 4$; 2.9%) and behavioral

changes ($n = 3$; 2.2%). Considering long COVID definition, 170 patients were evaluated at 12 and/or 24 weeks, with 30 (17.6%) having persistent symptoms.

Factors Associated With Persistent Symptoms

The presence of a comorbidity increased threefold the risk of developing long COVID at 12 weeks (OR = 3.52; $P = 0.041$). This model was reproduced using a logistic regression ($P < 0.01$; Hosmer and Lemeshow: $\chi^2 5.3$; $P = 0.725$). At 24 weeks, those with more severe disease on admission ($P = 0.03$) and adolescents ($P = 0.031$) were more likely to report symptoms.

Persistent fatigue was one of the most frequently reported symptoms, being more common among adolescents ($P < 0.01$), obese patients ($P = 0.024$), and those with severe disease at admission ($P < 0.01$). Behavioral changes were more frequent among adolescent (11%; $P = 0.016$): anxiety, panic attacks and depressed humor.

DISCUSSION

Little is known about the prevalence, risk factors and the most common symptoms of long COVID in children and adolescents. In our study, patients were evaluated three times: 4, 12 and 24 weeks. We observed that 19.4% had symptoms at 4 weeks and 13.3% still had symptoms at 12 weeks. Therefore, >1 in 10 patients reported long COVID symptoms. Other studies showed that the prevalence varied considerably from 4% to 66%.^{8,9} This high variability is probably due to different data collection and populations studied.

Respiratory symptoms were more commonly reported in the first 4 weeks, whereas neuropsychiatric symptoms were more frequent at 12 weeks. In addition, fatigue is one of the most frequently observed symptoms. These findings are consistent with the literature where headache, fatigue, sleep disturbance, concentration difficulties are the main symptoms reported.^{9,10} Those with a higher probability of having persistent fatigue are adolescents, obese patients, and those with a severe disease at admission. This is probably because these patients were more inactive, and those with COVID probably became even more inactive, facilitating the recognition of fatigue. A large prospective study also found that obesity was associated with a higher risk of persistent symptoms.⁸ Besides that, in our patients, the risk factors identified for long COVID were older age and pre-existing comorbidity. One study found that older children (6–18 years) or those with severe disease have a higher risk of having long COVID.¹⁰ This highlights the importance of close follow-up in adolescents, obese patients and those with severe disease.

Our study had some limitations. First, this was a retrospective study with a limited sample size. Second, the appointment was performed by 3 doctors, with no predefined questionnaire; however, each patient was evaluated by the same doctor. Behavioral changes were ascertained according to parents' descriptions, which can be inaccurate. Additionally, we only collected data from the children who were re-evaluated. This may introduce a selection bias since those who came could be the ones who had a severe disease or more persistent symptoms. Finally, the absence of a control group makes it difficult to ascertain whether symptoms were only attributable to post-COVID.

CONCLUSION

In our cohort, a significant proportion presented with symptoms after COVID infection, with respiratory symptoms being more frequent in the first weeks, and neuropsychiatric symptoms over time. According to the definition, 17.6% had long-term COVID symptoms. Pre-existing comorbidities and obesity were risk factors for persistent symptoms, and adolescents were the group with the

TABLE 1. Prevalence of Persistent COVID Symptoms Reported at the Time of Appointment

	4 Weeks, N (%)	12 Weeks, N (%)	24 Weeks, N (%)
No. patients evaluated	144 (60.8)	134 (56.5)	136 (57.4)
Symptoms' persistency	28 (19.4)	18 (13.3)	9 (6.6)
Fever	0 (0)	0 (0)	0 (0)
Chronic cough	8 (5.6)	3 (2.2)	3 (2.2)
Rhinorrhea	9 (6.2)	1 (0.7)	0 (0)
Dyspnea	1 (0.7)	3 (2.2)	2 (1.5)
Anosmia	7 (4.9)	4 (3.0)	3 (2.2)
Dysgeusia	2 (1.4)	2 (1.5)	2 (1.5)
Anorexia	1 (0.7)	0 (0)	0 (0)
Vomiting	1 (0.7)	0 (0)	0 (0)
Diarrhea	5 (3.5)	2 (1.5)	0 (0)
Headache	0 (0)	2 (1.5)	1 (0.7)
Fatigue	13 (9.0)	10 (7.5)	4 (2.9)
Myalgias	0 (0)	0 (0)	0 (0)
Joint pain	0 (0)	0 (0)	0 (0)
Sleep disturbance	4 (2.8)	5 (3.7)	5 (3.7)
Behavioral changes	4 (2.8)	6 (4.5)	3 (2.2)
Concentration difficulties	2 (1.4)	3 (2.2)	1 (0.7)

greatest risk. Persistent fatigue is of the utmost importance. More studies are needed to clarify symptoms of long COVID in children and adolescents.

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