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ORIGINAL ARTICLE

Do children present signs and symptoms consistent with a post-COVID-19 syndrome?

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Keywords:
COVID-19,
Child,
Fatigue,
Inflammation.

Abstract

Objectives: To carry out a systematic review of the clinical manifestations of long-term COVID in children. **Methods:** The starting point was: "What are the clinical manifestations in children with long-term COVID syndrome?". A systematic literature review was conducted in SCOPUS, Embase, NCBI, and MedRxiv databases. Articles on the clinical picture of long-term COVID in the pediatric population were included, with the cohort, case-control, cross-sectional studies, and case reports published in 2020 and 2021. The selection and analysis were performed by four researchers independently, following the Preferred Reporting Items for Systematic Reviewers and Meta-analysis guidelines. **Results:** Reviewers identified 6,279 potential articles, of which 8 met the inclusion criteria. The sampling in the selected publications ranged from 1 to 2,500 participants, whose age range ranged from 3 months to 18 years. The most reported symptoms in long-term COVID were: fatigue, upper and lower respiratory tract symptoms, sleep disturbances, and neurological symptoms. The duration of these symptoms ranged from four weeks to eight months. Some articles also reported pediatric inflammatory multisystem syndrome (SIM-P) in the long-term COVID. **Conclusion:** Long-term COVID affects on average 15.5% of children after infection, lasting from 4 to 32 weeks. The main symptoms were fatigue and dyspnea, followed by musculoskeletal, respiratory, neurological, and sleep disorders. Furthermore, it was impossible to elucidate these cases risk factors and outcomes in this study.

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INTRODUCTION

In December 2019, the coronavirus epidemic emerged in the city of Wuhan in China and spread worldwide. The World Health Organization (WHO) declared it a pandemic on March 11, 2020. Sars CoV-2 infection classically presents as an acute respiratory syndrome. The disease has produced major impact in all countries, with more than 470 million confirmed cases worldwide and a death rate of approximately 1.3%. Brazil had 29,630,484 confirmed cases and 657,205 deaths by the disease by March 2022. (MS) In pediatric cases, the main symptoms found in patients aged 0 to 19 years are fever, cough, diarrhea, nasal congestion, and dyspnea. Outcomes were generally positive, with few complications described, predominantly in patients with comorbid conditions[1,2]. Da Oliveira et al. (2020)[3], in a systematic review, pointed out that the main risk factor for complications in children were congenital diseases, comorbidities and prematurity, while a meta-analysis described a higher chance of complications in children under one year of age. In 2020, 14,638 (2.46% of the total) children and adolescents aged 0-19 years were hospitalized for the disease, and 1,203 (0.62% of the total) died[4]. In January 2022, Covid-19 was the second leading cause of death in children aged 5 to 11 years in Brazil, with 1,449 deaths of boys and girls aged 0 to 11 years and more than 2,400 cases of multisystem inflammatory syndrome in children (MIS-C) associated with Covid-19 recorded since the beginning of the pandemic[5].

Due to the relevant increase in the number of cases, the onset of new SARS-CoV-2 variants, and the low vaccination rates in the pediatric population, studying the disease in this age group becomes even more relevant. The persistence of symptoms or the development of new symptoms related to SARS-CoV-2 infection after Covid is a growing problem that has unfolded in the form a multisystem syndrome, described under various terms, the most common being long Covid or post-Covid syndrome[1,4]. Especially in adults, persistence of symptoms, signs or clinical parameters for two or more weeks after Covid, without return to a healthy baseline, may potentially be considered long Covid[1,2]. Despite the different patterns of acute Covid in adults and children, signs and symptoms of long Covid intersect in the two age groups[2]. Although there is a growing body of literature on long Covid in adults, pediatric data are scarce.

The determination of factors associated with the risk of suffering with long-term effects of Covid-19, the need to expand the knowledge about long Covid, the identification of new variants of SARS-CoV-2, and the lack of studies regarding vaccination in the pediatric population make it increasingly pertinent to study this syndrome in pediatric patients. Establishing an integrated rehabilitation process that provides targeted interventions to ensure adequate growth and development for children is needed.

METHODOLOGY

This review started with the question "What are the clinical manifestations in children with long Covid?" based on the *Population, Intervention, Comparison, Outcome* (PICO) model, used in Evidence-Based Practice (EBP) and recommended for systematic reviews[6]. Systematic reviews are based on clear questions and use systematic and explicit methods to identify, select and critically evaluate relevant research. In this sense, we chose to use the PRISMA recommendation, a checklist with a flowchart and 27 items devised to help authors to improve the quality of their systematic reviews and meta-analyses[7].

Since the analyzed studies had diverse characteristics (Table 1) and heterogeneous populations, objectives, and methodological procedures, and did not refer to clinical trials, statistical analysis (meta-analysis) was not possible. After data analysis, the review enabled the establishment of considerations about the clinical manifestations of long Covid in children.

Data Source

Searches were performed in databases SCOPUS, Embase, and NCBI. The question "What are the clinical manifestations in children with long Covid?" was formulated based on the PICO (Population, Interest, Comparison, *Outcome*) model. The keywords used (children, long covid-19, post covid-19) were entered "into the Health Sciences Descriptors" (DeCS) in the English language with their equivalents in the Portuguese language. The descriptors were used with the following combinations: "*child*" or "*children*" and "*long Covid-19*" or "*post Covid-19*".

Eligibility Criteria

Cohort studies, case-control studies, cross-sectional studies, and case reports published in 2020 and 2021 in the SCOPUS, Embase, NCBI, and MedRxiv databases that addressed the signs and symptoms of long Covid in pediatric populations were included. The following were excluded: (1) Articles not written in English, Portuguese, or Spanish; (2) articles discussing a different topic; (3) publications that were not scientific articles; (4) articles that addressed only post-Covid behavioral changes; (5) articles with a non-pediatric population; (6) articles that addressed Covid symptoms lasting less than two weeks from onset.

Data extraction

The authors of this review used a *Microsoft Excel* version 2019 (*Microsoft Office* 365 ProPlus, Redmond-WA, USA) spreadsheet to collect the following data: article name, database of origin, authors, publication date, study design, population size, mean age/age, studied site/population, symptoms, time since acute disease, progression, criteria for multisystem inflammatory syndrome in children (MIS-C), other important data observed, and article links. In addition, the references of the articles includes in the systematic review were checked to

Table 1. Articles selected according to eligibility criteria

Author	N	Age	Symptoms	Time after acute phase	Progression	MIS-C criteria
Jonas F. Ludvigsson	5	9-15 years (m=12)	Fatigue, dyspnea, palpitations, or chest pain in 100%; headache, difficulty concentrating, muscle weakness, dizziness, and sore throat in 80%; abdominal pain, memory loss, depression, skin rash, muscle pain in 60%; remitting fever, sleep disorders, joint pain, diarrhea or vomiting, and hyper anesthesia in 40%; altered sense of smell and taste, reduced appetite, chronic cough, and numbness in 10%	6-8 months	Persistent fatigue, did not fully return to school; two patients needed to be examined by a cardiologist and another two were referred to a psychologist	Did not meet
Jonathan Broad et al.	70	3 months to 16 years	MIS-C (Royal College of Paediatrics and Child Health criteria) previously diagnosed by a multidisciplinary team	Indeterminate (hospitalization: mean 7 days)	46 patients referred to ICU; 32 required inotropics; 10 required ventilation; 1 died	Met
Faith Miller	175	0 to 17 years	Fatigue, upper and lower respiratory tract symptoms, dermatological involvement, and neurological symptoms (cognitive impairment, headache, mental confusion, and difficulty concentrating)	4 weeks or longer	Outcomes not described	Did not meet
Danilo Buonsenso	129	<18 years	3 patients developed MIS-C and 2 had myocarditis. The most common persistent symptoms were: insomnia, respiratory symptoms, nasal congestion, fatigue, muscle pain, joint pain, and difficulty concentrating	120 days or longer	Outcomes not described	3 children met the criteria
Thomas Radtke and Agne Ulyte	2500	6-16 years	Most prevalent symptoms: fatigue, headache, nasal congestion, cough, epigastric pain, sleep disorders, oversleeping, and difficulty concentrating	4 weeks or longer	Outcomes not described	Did not meet
Anil Kumar Singhi	1	9 years	MIS-C	Indeterminate	Discharged with low-dose aspirin and echo ordered after 2 weeks	Met
Leona Knoke et al.	70	11.75 ± 3.9 years	8 patients reported at least one respiratory symptom, of which 6 had progressing respiratory problems and 2 had persistent cough. 10 patients suffered from fatigue; 5 patients had both persistent respiratory symptoms and fatigue	More than 4 weeks	Outcomes not described	Did not meet
Ismail M Osmanov et al.	128	18 years and younger	Fatigue, sleep disorders, sensory impairment, gastrointestinal and dermatological events. Some presented with long-term neurological, respiratory, cardiovascular, and musculoskeletal disorders. 44 patients reported persistent symptoms from more than one category	6-7 months	Fatigue, altered sense of smell, altered taste, and breathing difficulties decreased over time. No change was observed in sleep disorders or headaches over time	Did not meet

avoid data duplication bias. The methodological quality of the selected cross-sectional studies was assessed based on the modified Newcastle-Ottawa Scale for cross-sectional studies.

RESULTS

The 6,279 articles initially identified in the Embase, Scopus, NCBI, and MedRxiv databases were divided among the authors. The first step in the selection process led to the exclusion of 6,238 articles that did not present a subject in line with the objectives of the present review. Then, duplicate articles that did not meet the eligibility and inclusion criteria were removed. In the end, eight publications were included in the systematic review: two case reports, four cohort studies, and two cross-sectional studies (Figure 1).

The articles were written in different places around the world, two in the UK and the others in Italy, Sweden, India, Russia, Germany, and Switzerland. Their populations included individuals aged three months to 18 years. The sizes of the populations ranged from one to 2,500 individuals.

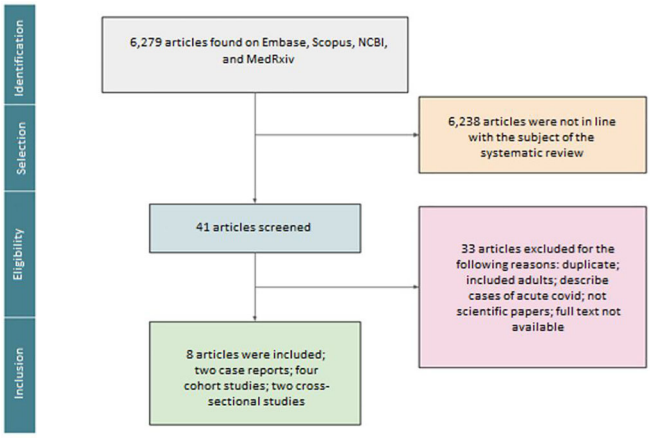


Figure 1. Flowchart showing the number of articles found and selected for analysis after the application of inclusion and exclusion criteria.

The study conducted in Sweden by Ludvigsson (2021)[2] presented a series of five cases of children with symptoms persisting for six to eight months after Covid. Four in five patients were females, their mean age was 12 years, and only one child had previous comorbid conditions, namely asthma, allergies, and autistic spectrum disorder. In addition, a systematic review was performed, but none of its articles was selected because they did not address the topic of long Covid.

Some studies described cases of multisystem inflammatory syndrome in children (MIS-C) due to SARS-CoV-2 infection. Broad et al. (2021)[8], in a study conducted in London, UK, presented 70 cases of MIS-C and correlated higher incidence of disease with individuals from ethnic minority groups. In turn, Buonsenso et al. (2021)[9], in an Italian study of 129 children, found three cases of MIS-C. The authors also reported that more than half of the children were symptomatic after more than 120 days of diagnosis.

The most commonly reported symptoms in children with long Covid were fatigue, upper and lower respiratory tract symptoms (cough, runny nose, nasal congestion, etc.), sleep disorders, and neurological symptoms (difficulty concentrating, headache, and cognitive impairment). Three of the eight articles also described persistent dermatological involvement such as skin rash. Similarly, three studies also described persistent gastrointestinal symptoms such as vomiting, diarrhea, and epigastric pain. Although less cited, musculoskeletal symptoms such as joint and muscle pain were also observed.

The prevalence of long Covid symptoms in the selected cohort studies ranged from 9.5% to 52.7%, with a mean prevalence of 15.5%. Among all studies, the most prevalent signs/symptoms were fatigue and dyspnea, reported in all selected articles. Sleep disorders, neurological alterations such as difficulty concentrating, and dermatological alterations such as skin *rash* were described in 50% of the articles. The longest duration of symptoms observed was eight months, with a minimum duration of four weeks.

DISCUSSION

Despite the paucity of information about long Covid in children, especially in Brazil, several countries have reported a significant number of cases. In the United Kingdom, 12.9% of children aged 2 to 11 years and 14.5% of children aged 12 to 16 years have persistent symptoms after five weeks of infection onset[10]. There is also information from the *Office for National Statistics* (ONS) that in the UK, around 79,000 cases of long Covid occurred in patients under the age of 19[11,12].

Regarding the age of children with long Covid, older age appears to be a risk factor for the development of the condition. In a prospective cohort study conducted in Russia in 2021, children between the ages of 6 and 18 years were most affected by post-Covid symptoms. Furthermore, in the UK, studies have also described a higher incidence of persistent symptoms as age increased. Females are also more prone to developing post-Covid symptoms, a finding not analyzed in the articles included in this review[9,13,14].

In the present review, the most frequent symptoms presented by children with long Covid were fatigue, upper and lower respiratory tract symptoms (cough, runny nose, nasal congestion and etc.), sleep disorders, and neurological symptoms (difficulty concentrating, headache, and cognitive impairment), which corroborates with data published in other studies on long Covid in the pediatric age group. In the prospective cohort study conducted in Russia, 126 of 518 children had fatigue, sleep disorders, and sensory alterations as the main findings of long Covid[13].

The symptoms that characterized long Covid in the early studies and reports about the condition were fatigue, myalgia, arthralgia, headache, insomnia, and respiratory and cardiovascular alterations. As the studies evolved, more than 100 symptoms have been described, including gastrointestinal alterations, seizures, hallucinations, and others. Thus, there is still no well-defined characterization of the persistence of symptoms and sequelae from Covid, a fact that was noted in this review, which found a wide variety of signs and symptoms characterized as post-Covid syndrome. However, there is evidence that children and adults present with similar symptoms in this situation[11,12,15].

Another condition found in our analysis was multisystem inflammatory syndrome in children (MIS-C), a disease with similar clinical and workup test changes to Kawasaki disease, incomplete Kawasaki, and/or toxic shock syndrome. Individuals with MIS-C, also a post-infection syndrome, develop more severe symptoms. MIS-C has well-described diagnostic criteria. For the *Centers for Disease Control and Prevention* (CDC), individuals with MIS-C must have had SARS CoV-2 infection, seroconversion, or Covid exposure within four weeks pf the onset of symptoms. Diagnostic criteria differ among health agencies such as the CDC and the WHO, but are based on fever, inflammation, prior hospitalization, organ system

involvement, exclusion of other causes of infection, and SARS--CoV-2 exposure or infection[16,17].

There is great variation in the duration of post-Covid symptoms in the literature, with some authors describing symptoms lasting for more than five months[13] and others reporting symptoms persisting for up to twelve weeks[10]. Our review also observed some variability, with durations of at least four weeks and symptoms persisting for as long as eight months from the onset of SARS CoV-2 infection.

In this review, a large portion of the studies did not report the long-term outcomes of long Covid. Some children had persistent symptoms until after the time of publication of the review and some required follow-up with specialists, such as cardiologists and psychologists. MIS-C cases required more intensive care, case-specific medications, high complexity tests, and follow-up with specialists after discharge. Outcomes reported in literature vary widely. According to a study conducted in the Netherlands in which information was collected from pediatricians about their experiences with long Covid, 36% of 89 children had severe functional limitations [12]. However, other authors reported complete cessation of symptoms within 12 weeks[10].

In the adult population, it is estimated that 80% of the patients infected with SARS-CoV-2 develop one or more long-term symptoms[18]. In the pediatric population, on the other hand, there is a great deal of variation among studies about the prevalence of long-term Covid symptoms, and it is important to note the small number of papers with this age group, especially papers with larger sample sizes.

Importantly, the long-term consequences of SARS--CoV-2 infection in children and adults are similar. According to Willi et al (2021)[19], the predominant symptoms of post-Covid syndrome in adults are fatigue and dyspnea, affecting 39% to 74% of the population. In addition, meta-analyses on long term Covid in adults also indicate fatigue (38% to 58%), dyspnea (24% to 32%), headache (44%), and cough (13%) as some of the most prevalent symptoms in this condition (18,20). This finding agrees with Ludvigsson (2021)[2], who reported fatigue and dyspnea in 100% of children and adolescents aged nine to 15 years.

There is great similarity in the neuropsychiatric symptoms presented by the two age groups. In meta-analyses by Krishnamoorthy et al. (2020)[21] and Premraj et al. (2022)[22] (21,22), sleep disorders, anxiety, and depression were the main symptoms in adults. In children, neuropsychiatric manifestations gain more relevance, given their influence on global development.

Some studies show that MIS-C presents in a very similar way to multisystem inflammatory syndrome in adults (MIS--A)[23,24]. However, long Covid in children and in adults has its differences. According to the literature, long Covid in children seems to affect mostly girls[13,14], while in adults the situation remains controversial, with diverging reports claiming preferential involvement of males or females alike[19].

The long-term outcomes of Covid are still being discussed in the literature. In adults, several studies have demonstrated decreases in functional capacity and health-related quality of life associated with long-term Covid (36% and 52% respectively)[20], with almost a third of adults not returning to their baseline functionality 12 months after disease[25,26]. However, in children, the evaluation of this topic is still lacking despite its clear relevance.

The persistence of symptoms in children may have a far greater impact than anticipated. The presence of musculoskeletal, respiratory, neurological, and many other symptoms may, for example, strongly affect the school, athletic, and social performance of these individuals. A multinational study developed on an online platform, known as the "*Long COVID Kids Rapid Survey 2*," found significant changes in children's physical activity performance after infection with SARS CoV-2, showing that most were not able to maintain the same level of fitness. About 20% were no longer able to enjoy physical exercise, and 30% experienced worsening symptoms after engaging in physical activity. These findings are very relevant, since the practice of physical activity is essential for the growth, development and socialization of children[27].

Neuropsychiatric symptoms may severely affect the life and development of children. Most studies have found the persistence of symptoms such as lack of concentration, difficulty processing information and understanding instructions, and recent memory loss. All of these symptoms can significantly impact school performance and jeopardize their academic and professional lives in the long term[2,8,9,14,28,29].

The importance of studying long Covid in the pediatric population is not limited to understanding what the main symptoms are and what they cause, but also involves understanding who are the individuals most susceptible to persistent symptoms. A prospective cohort study conducted in Russia showed that age is an important risk factor. Children aged 6 to 11 years had more persistent symptoms, about twice as many compared to children under the age of two. Similarly, adolescents between 12 and 18 years old also showed higher chances of developing long Covid. Another relevant risk factor is association with a history of allergic diseases. Allergic rhinitis, asthma, and food allergies were the comorbid conditions most commonly found in these patients. In addition, obesity and overweight were also seen as risk factors in children aged 6 to 11 years, as well as severe cases of acute Covid. However, studies on the risk factors for long Covid in pediatric populations are still scarce in the literature and lack solid information that might improve the management of these cases[14].

Thus, although the number of studies investigating post-Covid syndrome in pediatric populations is increasing, there is no agreement over how this new disease might be defined and diagnosed in clinical practice or which relevant outcomes should be measured[30]. Furthermore, literature on risk factors, outcomes of long-term Covid, age segregation among children and adolescents, nationwide approaches, and

other aspects of long-term Covid studies are lacking. There is an urgent need to optimize and standardize outcome measures for this important age group, both for clinical and research reasons, to thus allow the pooling of data, comparisons across different geographic locations, and the practical application of these findings converted into multidisciplinary management protocols designed to address long Covid in children and morbidity prevention measures.

The lack of studies about long Covid in the pediatric age group has an important impact on the management of Covid in children. Specifically in Brazil, very little has been discussed about this subject. The fact that most children present with mild SARS CoV-2 infection may have led to an underestimation of the cases developing persistent symptoms and even reinforced the lack of actions aimed at the urgent vaccination of this population. A study of 510 children with long Covid in the UK showed that only 10% of them returned to their usual level of daily activities after SARS CoV-2 infection. Therefore, in order to maintain quality of life and avoid future health problems, vaccination and follow-up of children with Covid is paramount[9].

Our study found that persistent Covid symptoms affect an average of 15.5% of children after the onset of infection, and last from four to 32 weeks, affecting all age groups. The main symptoms observed were fatigue, upper and lower respiratory tract involvement, neurological symptoms, and sleep disorders. Therefore, it is clear that pediatric populations are vulnerable to long Covid and may have significant involvement by SARS-CoV-2 infection. Associated risk factors and outcomes remain unclear.

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