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Research Article

Role of Symptoms in Acute Sars-CoV2 Infection in Developing Long-Covid in Pediatric Age

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Abstract

Background: In children, acute SARS-CoV-2 infection is often asymptomatic or paucisymptomatic, but the symptoms present in the post-COVID phase (long COVID) are increasingly worrying. The pathophysiology and the correlation with acute infection are still unclear. Therefore, our study had the objective of correlating the symptoms of long COVID with patient's medical history, in particular with the symptoms of the acute phase of infection.

Methods: We analysed the medical history of 118 pediatric patients evaluated for long COVID. As a comparison group, we used patients with a previous history of Multisystem Inflammatory Syndrome in Children (MIS-C), as an example of inflammatory manifestation related to SARS-CoV2.

Results: No correlation with gender or risk factors emerged. Severity of symptoms in the acute phase or history of inflammatory complications (MIS-C) do not correlate with the risk of developing long COVID. A significant correlation emerged between vaccines for SARS-CoV-2 infection and arthromyalgia: vaccinated patients showed arthromyalgia less frequently than non-vaccinated (23.2% vs 51%, p = 0.002).

Conclusion: It is still difficult to establish whether these symptoms are caused by the infection or if they are a psychological consequence of social restrictions imposed by pandemic. Apparently, vaccination reduce the risk for developing arthromyalgia after the infection.

Introduction

On 11th March 2020, the World Health Organization defined the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection as pandemic, and to date has caused significant mortality and morbidity worldwide [1]. Generally, children are less severely affected by COVID-19 than adults are, and the acute infection is often asymptomatic or paucisymptomatic [2]. Actually, the scientific community is focusing on long term complications of COVID-19. In children and adolescents, in particular, there are two main complications described: MIS-C (Multisystem Inflammatory Syndrome in Children) and long COVID. MIS-C, an acute and potentially fatal condition that may develop after 2 to 6 weeks after the SARS-CoV-2 acute infection, was predominant in the first period of pandemic. Numerous studies and research projects have been conducted on this topic, especially on its pathogenesis, with most of the hypotheses pointing to cytokine storm [3]. Children with MIS-C present with

several multisystemic manifestations and multiorgan involvement. The most common organs involved are gastrointestinal tract, skin, mucous membranes, and cardiovascular system [4], rarely leading to severe health complications and death [5]. Nevertheless, in the last year, cases of severe inflammatory forms have decreased in children; contextually, a progressive increase in the number of children with persistent or recurrent symptoms after SARS-CoV-2 infection has been noted. This condition is defined with the term "long COVID", a spectrum of signs and symptoms that continue or develop after acute COVID-19, and are not explained by an alternative diagnosis, despite the negativization of the diagnostic test for COVID-19. According to National Institute for Health and Care Excellence (NICE) guidelines, long COVID includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks after acute COVID-19) and post-COVID-19 syndrome (12 weeks or more after acute covid-19) [6]. Long COVID has been widely studied in adults [7]. Most frequent symptoms of long COVID in adults are fatigue and dyspnea; other less typical symptoms, like cognitive and mental disorders, headache, myalgia, joint pains, smell and taste dysfunctions, cough, hair loss, insomnia, wheezing, rhinorrhea and cardiac and gastrointestinal issues have been described, reflecting the wide variety of clinical manifestation and the involvement of multiple organs. These symptoms may persist for up to six months with a heavy impact on daily activities and quality of life [8,9,10]. The pathophysiology of long COVID is still under debate, speculating on tissues' long-term damage, persisting viral-induced inflammation, immune dysregulation, autoimmunity, diffuse endothelial damage and micro thrombosis [11]. On the other hand, the pandemic and the resulting restrictions have had an important impact on both the physical and mental health of children. Therefore, it may be difficult to estimate the prevalence of long COVID and distinguish how much the symptoms manifested by children are linked to a previous infection or the consequences of the lockdown and changes in daily life caused by the pandemic. It is not clear if the severity of the primary infection affects the probability of developing long COVID [12]. Some studies did not find any association between long COVID and initial disease severity during acute COVID-19; however, patients admitted to ICU apparently are more likely to suffer long-term symptoms compared to other patients [8], even if it is difficult to distinguish how much these symptoms are related to COVID-19 or to the permanence in ICU itself (post-intensive care syndrome or exacerbation of pre-existing health conditions). Only few studies have addressed the long-term recovery from COVID-19 in children; most of these studies include small sample sizes and lack of a control group [13,14]. For this reason, it is difficult to reach a uniqueconclusion on the subject, and it may be difficult to distinguish long-term symptoms caused by SARS-CoV-2 infection from "pandemic-related symptoms". As the Pediatric Reference Center for COVID-19 in Lazio region (Italy), we managed over 1800 admissions of patients with acute SARS-CoV-2 infection or its complications, and about 400 patients were followed as outpatients. During our practice, we observed an increasing number of patients with persistent post COVID symptomatology, so we tried to describe patients who fulfilled the criteria for long COVID and secondarily, to correlate the presented symptomatology with the patient's medical history. In addition, another objective was to compare this group of children with the group of patients who were hospitalized for MIS-C to evaluate the prevalence of long COVID in these patients who have had severe inflammatory complication of SARS-CoV2 infection.

Materials & Methods

This is a retrospective observational study on patients evaluated for persistent symptoms after SARS-CoV-2 infection. The inclusion criteria were:

- pediatric (less than 18 years) age;
- previous SARS-CoV2 infection;
- presence of severe post-COVID symptoms (persistent fever, severe chest or abdominal pain, dyspnea) or persistent symptomatology (asthenia, headache, arthromyalgia, fever, cough, dyspnea, exercise intolerance, chest pain, anosmia and ageusia, abdominal pain, pattern change, dizziness, weight decreased, sleep and behavior disorders) for more than 4 weeks;
- No other possible clinical explanations for the symptoms (in particular, excluding possible concomitant infections or compelling diseases).

We included hospitalized patients and outpatients who fulfilled the inclusion criteria from 1st June 2020 until 30th October 2022. These symptoms were evaluated in terms of prevalence by different factors (gender, comorbidity, previous vaccination, previous hospitalization, therapy performed, and any reinfections) and previous MIS-C. Patients' data were collected anonymously, and encoded on an electronic database (Excel). Considering the retrospective nature of the analysis, the current study did not require the approval of the local ethics committee, but according to current legislation a notification was sent. Data were retrospectively analyzed in line with personal data protection policies. Statistical analyses were performed using IBM SPSS Statistics Version 22 for Windows and the online service OpenEpi (available at http://openepi.com/Menu/OE_Menu.htm). Missing data points or data that did not apply to the analysis were excluded. Categorical variables are presented as frequencies and percentages, quantitative variables are presented as means (standard deviation), or median (range), as appropriate. Categorical variables between groups were compared with Chi2 test or Fisher-exact test. The means of the two different groups were evaluated by two sample unpaired t-tests if continuous variables were normally distributed.

A p-value <0.05 was considered statistically significant. The diagnosis of previous infection was established in the presence of at least one respiratory specimen positive for SARS-CoV-2 (RT-PCR or antigen detection) or through detection of positive serology (immunoglobulin M and immunoglobulin G against SARS-CoV-2). The clinical informations ware collected from the clinical records and the ambulatory evaluations carried out at our clinic. As a control group, we involved patients admitted to our department for MIS-C from 1st June 2020 until 30th October 2022. These patients, according to the internal protocol of our department, were followed up to 3, 6, and 12 months after the hospitalization, so we could observe any new sign or symptom related to the previous infection. Due to its retrospective nature, this study could not evaluate the possible role of different SARS-CoV-2 variants. The recent discover of Long COVID in pediatric age and its stringent criteria, constitute a limitation to our sample size.

Results

Our population included 118 children, with a mean age of 11.3 years (SD 3.238, range 4-18 years), of whom 58 (49%) were female. Most patients had no other known comorbidities (see Table 1 for details), except neurocognitive disorders (5.9%), asthma (4.2%), obesity (2.5%), prematurity (2.5%), and others (11%). The neurocognitive disturbances include Specific Learning Disorders (2), depression (2), anxiety issues (4) and compulsive-obsessive disorder (1). The other disorders include autoimmune diseases (2 patients with celiac disease and 1 scleroderma), adenoid hypertrophy and migraine. Before the infection, about 13.6% of the children had received at least one dose of SARS-CoV-2 mRNA vaccine. From the information available, the family cluster represented the primary source of infection (32.2%) while in 60.7% of cases the source is unknown. About 5% of children had experienced previous stressful situations (mourning; long hospitalizations etc.); anyway, there is no difference in clinical presentations compared to the other patients in the cohort. The mean time length of negativization from SARS-CoV-2 infection was 17.6 ± 10.3 days. In our cohort, 17% of children had an asymptomatic infection. Overall, only 5.1% had severe symptoms (i.e. dyspnea, chest pain, alterations of vital parameters, etc.), while the majority manifested mild symptoms (77.9%) during the acute phase and the mean duration of symptoms was 6.1 ± 6.2 days. In the acute phase of the infection, no treatment was necessary in 56.8% of the cases; symptomatic therapy was used in 16.1% and antibiotic therapy in 11.9%. Only 19.4% required hospitalization, with the use of antiviral drugs (Remdesivir) in two cases (1.6%) and oxygen therapy in one case (0.8%). The most frequent symptoms of long COVID reported are described in Figure 1. In our cohort, in most cases (72.9%) patients had only one episode of SARS-CoV-2 infection. About 31.4% performed regular physical activity before the infection and only 25.4% continued after; therefore 6% did not resume sport after the infection. Respiratory symptoms such as dyspnea and cough were reported in 16.9% and 6.8%, respectively, whereas gastrointestinal involvement included abdominal pain (24.6%) and irregular bowel movements (10.1%). Anxiety and behavioral disorders (not present before the infection) were more frequent in patients with known comorbidities (40.6% vs 22.1%, p = 0.048 and 34.4% vs 17.4%, p = 0.044 respectively). Prior immunization for SARS-CoV-2 had an impact on the presence of arthromyalgia, probably as a protective factor; in fact, patients who had not been vaccinated showed arthromyalgia more frequently than vaccinated children (51% vs 23.2%, p = 0.002). No other differences in the prevalence of symptoms have been observed among patients. Among our control group of 54 children hospitalized for MIS-C (of whom 27 needed management in our Intensive Care Unit), only 5 patients (9.3%) developed Long COVID symptoms (3 of them required intensive care). All these five patients presented asthenia as a predominant symptom, similarly to non-MIS-C patients. Globally, the reported symptoms resolved within 3 months in 38.1% of the sample, in 20.3% between 3-6 months and in 33% more of 6 months. The remaining 8.6% is unknown. Most patients (82.2%) did not receive treatment for the symptoms reported.

Total	N = 118
Age (mean ± SD)	11.3 ± 3.2
Female	58 (49%)
Comorbidities	
None	86 (72.8%)
Asthma	5 (4.2%)
Obesity	3 (2.5%)
Prematurity	3 (2.5%)
Neurocognitive disorders	7 (5.9%)
Exposure to stressful events	6 (5.1%)
Others	13 (11%)

Table 1: Cohort demographic characteristics and comorbidities prevalence. SD standard deviation.

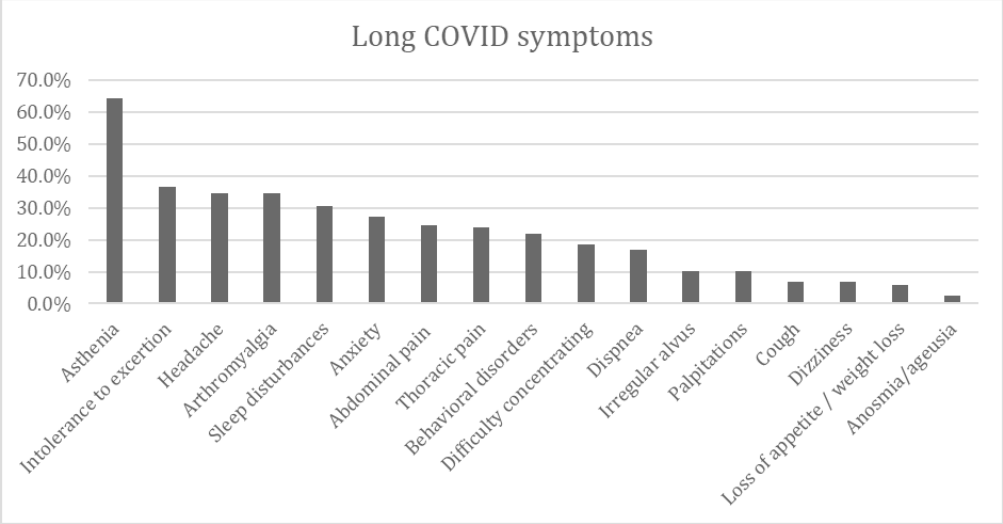

Figure 1: Prevalence of Long COVID symptoms.

Discussion

The clinical manifestations of long COVID are highly variable in terms of symptoms, intensity, and duration. They can present alone or in combination, can be transient or intermittent, can change over time, or remain constant. Our study confirmed that the presentation of symptoms is extremely variable. According to the literature, asthenia is the most frequently reported symptom, with other clinical manifestations such as headache and arthromyalgia [15]. The underlying mechanisms causing the various clinical spectrum of long COVID are still unknown. At the moment, neither from this study nor from reading the literature on this issue it is possible to conclude whether the etiopathology is inflammatory, related with acute infection, or whether it is linked to the psycho-social complications caused by pandemic. From our observations, we could suggest that the severity of symptoms in the acute phase or history of inflammatory complications (MIS-C), despite the need for long hospitalization or permanence in Intensive Care Unit, is apparently not correlated with the risk of developing long COVID's symptoms. It is also remarkable that a large part of our cohort was asymptomatic or mildly symptomatic in the acute phase of the infection, without need for treatment. No correlations with risk factors emerged, while studies on adults report female sex and prior psychiatric disorder (like anxiety or depression diagnosis) as risk factors to develop long COVID [16]. We had a similar result in our cohort, but the small sample size and the lack of a structural psychological evaluation do not allow us to make conclusions on this issue. These findings appear to support the role of the pandemic and social isolation as a relevant cause or cofactor in the onset of symptomatology. The lockdown, the social distance, and the inability to play sports and go to school had a strong impact on the population, especially on adolescents. As confirmed by the study by Borch et al [15], the risk of developing symptoms similar to those of long COVID was higher in the children who did not have COVID-19. Therefore, we cannot define them as long COVID symptoms, but rather as symptoms related to the social consequences of the pandemic. So, given the difficulty in discerning whether the problem is organic or psychological, NICE guidelines suggest performing a complete screening to exclude organic causes in children who presents with long COVID symptoms, suggesting psychological support to all children if the screening is negative [6]. As indicated by the good practices statement of Italian Higher Institute of Health [17], we applied a similar approach to the patients evaluated in our hospital, offering psychological evaluations and, when needed, specialistic support and treatment, to most of our patients. As a final consideration, long COVID syndrome is not the only post viral syndrome that we know. Symptoms of fatigue, myalgia and psychiatric issues have been described in survivors of Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) for up to four years [8]. In particular, MERS survivors suffered from chronic fatigue and mental health problems even more than 1 year after the acute infection [18], and chronic post-SARS is characterized by persistent fatigue, diffuse myalgia, weakness, depression, and nonrestorative sleep [19]. There is evidence of depression, anxiety, fatigue, and post-traumatic stress disorder in the post-illness stage of previous coronavirus epidemics but it is difficult to separate the effects of the infection from the impact of an epidemic on the population [20]. Maybe Coronavirus itself could have a direct role in causing these post-viral long-term symptoms, resulting in chronic post-inflammatory central nervous system pathologies that adversely affected sleep, pain sensitivity,

and energy [18]. Now, there is no defined treatment or specific therapy for long COVID patients, so the only weapon we have available is the prevention of the infection and its consequences. Recent evidence on vaccination against SARS-CoV-2 suggests that vaccines reduce the risk of long COVID by lowering the chances of contracting COVID-19 in the first place. However, for those who do experience a breakthrough infection, the vaccination might only halve the risk of long COVID, or have no effect on it at all [21]. Our findings apparently confirm the hypothesis of a protective role, suggesting a reduced risk of developing symptoms conferred by the immunization.

Conclusions

Bearing in mind that COVID-19 in children has been underestimated and that the characteristics of long COVID are variable in both incidence and clinical presentation, it is difficult to draw definitive conclusions on the topic. Awaiting further research that could evaluate the direct impact of SARS-CoV-2 on neurological tissues and the impact of vaccination in preventing the long-term effects of the infection, we suggest the implementation of social and psychological facilities for patients with persistent symptoms. We also reinforce the indication for vaccination in children, to reduce the possible infections and end as early as possible the SARS-CoV-2 pandemic.

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Author Contributions: AS and AC designed the study and critically revised the manuscript; AS, MTR, ME and EC revised the clinical charts, collected the data, performed the statistical analysis and wrote the manuscript; CM, REP, SS, PS gave substantial contribution for the interpretation of the results. All the author revised and approved the final version of the manuscript.

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Consent statement and other Ethics Statements: Considering the retrospective nature of the analysis, the current study did not require the approval of the local ethics committee, but according to current legislation, a notification was sent. Data were retrospectively analysed in line with personal data protection policies. All data were revised anonymously, so no consent was required.

Data Availability Statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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