Review Article

Advances in researches on long coronavirus disease in children: a narrative review

Jiaqian Zhang[#], Taiji Kuang[#], Xinglou Liu^

Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xinglou Liu, MD, PhD. Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095, Jiefang Avenue, Wuhan 430030, China. Email: liuxinglou@163.com.

Background and Objective: In the context of the global pandemic of coronavirus disease 2019 (COVID-19), more than 700 million infections and millions of deaths have occurred in countries around the world. Currently, two main sequelae of this disease are considered to occur in children, namely, multi-system inflammatory syndrome in children and long COVID. Among these two, the incidence of long COVID is higher and its impact on the population is more extensive, which is the focus of us. However, due to the lack of relevant studies and the limitations of most studies, the studies on sequelae of COVID-19 infection lag behind those of adults, but they have begun to attract the attention of some clinicians and researchers. We aim to summarize the current knowledge of long COVID in children, helping pediatricians and researchers to better understand this disease and providing guidance on research and clinical treatment of it.

Methods: We reviewed all the studies on "long COVID", pediatric, children, adolescent, post-COVID syndrome in PubMed published after 2019.

Key Content and Findings: This review summarizes the latest researches on epidemiology, pathogenesis, clinical manifestations, prevention and treatment of long COVID in children. Based on the existing research data, we summarized and analyzed the characteristics of long COVID in children, discovering the means to decipher the diagnosis of COVID-19 in children and some potential therapeutic treatments.

Conclusions: We aim to summarize existing research on long COVID in children and help pediatricians and government agencies quickly understand the disease so that it can be used for clinical diagnosis, treatment and prevention in the population. In addition, providing a research basis for further researches on the cellular and even molecular level to explain the occurrence and development of diseases, and has a guiding role for future research direction.

Keywords: Coronavirus disease 2019 (COVID-19); long COVID; children; post-acute sequelae of COVID-19; pediatrics

Submitted Sep 08, 2023. Accepted for publication Dec 31, 2023. Published online Feb 23, 2024.
doi: 10.21037/tp-23-472
View this article at: https://dx.doi.org/10.21037/tp-23-472

^ ORCID: 0000-0003-1214-1444.

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). With the continuous variation of SARS-Cov-2, its infectivity gradually increased, causing a global pandemic. Compared with adults, the children COVID-19 patients usually have milder symptoms and a lower rate of severe cases, but the consequences of sequelae can be more profound in children (1-4). Long COVID and multi-system inflammatory syndrome in children (MIS-C) were two main sequelae of COVID-19 reported in children currently, and long COVID has a more widespread effect.

Long COVID is a multi-system syndrome characterized by fatigue, headache, mood disorders, reduced sense of smell and other symptoms (3,5). In March 2022, the Delphi Consensus statements put forward the official definition of children with long COVID: post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with one or more persisting physical symptoms for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis (6). The symptoms have an impact on everyday functioning, may continue or develop after COVID-19 infection, and may fluctuate or relapse over time. At present, studies on long COVID mainly focus on adults, while there are few studies on children, so pediatricians have insufficient understanding of it. Therefore, this article will review the epidemiological characteristics, pathogenesis, clinical manifestations, diagnosis and treatment of long COVID in children based on the existing studies of pediatric cases. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-472/rc).

Methods

We comprehensively evaluated multiple types of studies on long COVID in children using PubMed and using "Long COVID", "Children", "Pediatric", "treatment", "pathogenesis", and "epidemiology" as keywords. Inclusion criteria included the following article types: narrative review, meta-analysis, case report, case series, and original article. Exclusion criteria included non-human studies; studies not available in English. Two authors reviewed the search results and completed a manual full text review. The methods of research used in this narrative review are detailed in *Table 1*.

Epidemiology of long COVID

During the SARS-CoV-2 pandemic, large-scale infection hit most countries in the world, with an explosive spread and a strong infectivity. The morbidity and severe cases rate of adults were higher than those of children, and the severe cases rate and mortality of patients with underlying diseases were higher. The morbidity of long COVID ranges from 1.6% to 70%, corresponding with the prevalence of countries, population vaccination coverage, and the reliability and comprehensiveness of relevant statistics (3,7-12). People are generally susceptible to SARS-Cov-2 and can gain immunity after vaccination. However, due to the strong mutation and variation ability of SARS-CoV-2, at most time, the vaccine is only effective in reducing the severe cases rate during the acute phase, but has little help in reducing the primary case morbidity (13). Moreover, the latest studies in children have found the function of SARS-CoV-2 vaccine in reducing the morbidity of long COVID (11,14). And other factors, including obesity, age, gender, race, medical history like allergies, severe acute-COVID-19, living environment factors, levels of inflammatory markers *in vivo* after disease, whether having mental problem and dysphrenia before infected all may play a role in the susceptibility to long COVID, could be used as susceptibility factors to guide the prevention of long COVID after the treatment of primary SARS-CoV-2 infection (2,7,10,15).

Pathogenesis of long COVID

Both in adults and children, the underlying pathogenesis of long COVID remains unclear. The current studies on the mechanism of COVID-19 predominantly rely on adult clinical studies due to ethical considerations, limited availability of tests, and the relatively smaller number of studies involving children. However, some limited clinical studies have found similar results in children and adults, suggesting that the pathogenesis of COVID-19 may be similar in both age groups. The virus persists in some tissues of the body, but it is not sufficient to cause typical clinical manifestations and can form viral reservoirs *in vivo*. In clinical studies in children and adults, viral RNA and protein can still be detected 2 months after acute infection in some patients, and there is a certain correlation with

Table 1 The search strategy summary

Items	Specification
Date of search	September 7, 2023
Database searched	PubMed
Search terms used	"Long COVID", "Children", "Pediatric", "treatment", "pathogenesis", and "epidemiology"
Timeframe	2019 to 2023
Inclusion and exclusion criteria	Included article types: narrative review, meta-analysis, case report, case series, original article
	Exclusion criteria included non-human studies; studies not available in English
Selection process	Independently selected by authors

COVID, coronavirus disease.

the symptoms of long COVID (16-19). Furthermore, the activation of herpes virus such as Epstein-Barr virus (EBV) from latent state may also be one of the potential mechanisms (20). A large-scale immunological study has shown that the viral antigen activity of the long COVID group is higher than that of the control group (21). Although the specific mechanism by which EBV induces long COVID has not yet been identified, the association between EBV and multiple immune system-related diseases gives us reasons to believe that the elimination of EBV could be one of the potential therapeutic targets. Antibodies against viruses cross-react with other tissues in the host, similar to the cross-immune response of streptococcal infections to the kidney and heart valves. In the field of viral antibodies, there is little evidence to confirm this conclusion. It is generally agreed that cross-immune reactions only exist between viruses of the same serotype or adjacent species. It has been found that intestinal flora may also mediate cross-immune responses against SARS-CoV-2 spike protein S2 (22-26). The persistent disorder of inflammatory response after recovery may also be one of the causes, mainly showing in the up-regulated expression of inflammatory factors in the body. And because SARS-CoV-2 may persist in the body, immune system could be continuously irritated, leading to periodic or persistent elevation of inflammatory cytokines (1,12). Coagulation dysfunction and vascular endothelium damages are caused by the interaction of the virus with the ACE2 receptor, triggering continuous thrombotic vasculitis and activation of the clotting cascade effect. Many investigations have shown that the levels of D-dimer, interleukin-6 (IL-6), interleukin-1 (IL-1) and other cytokines in children with long COVID are elevated, suggesting the risk of inflammation and thrombosis in their bodies (1,2,27-29). Tissue and organ damages can be driven by these inflammatory cytokines during the acute phase of infection and persist after recovery. Pathological investigations have found that the virus accumulates in multiple organs of the human body and may exist for a long time, but the degree of damage to different organs varies greatly. Particularly, severe organ damage is less in children in the acute stage, and children without MIS-C can also manifest multisystem symptoms (1,30). In addition, autonomic dysfunction has been suggested as a potential mechanism for the development of cardiovascular symptoms and symptoms resembling myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in individuals experiencing long COVID (31-33).

Clinical manifestation of long COVID in different system

The clinical manifestations of long COVID in children closely resemble those observed in adults, exhibiting a diverse range of symptoms that can affect multiple bodily systems. These symptoms may include fatigue, headache, hyposmia, hypogeusia, muscle or joint pain, insomnia, cough, cognitive difficulties, fever, dizziness, abdominal pain, dyspnea, post-exertional malaise, and decreased exercise tolerance (7,34-38) (*Table 2*). Fatigue (2–87%) and headache (3–80%) were the most common symptoms reported in numerous reports (3,12). These symptoms implicate multiple systems, and their severity is influenced by various risk factors. A survey conducted in Italy revealed that 92% of patients with long COVID experienced difficulties in their daily lives to varying degrees, with 29% of them requiring assistance from a multidisciplinary team (35).

Table 2 The clinical manifestation

Systems	Symptoms	Mechanisms
Respiratory system	Dyspnea, chest tightness or pain, cough, exercise intolerance, post-exertional malaise	Vagus nerve disorder, virus persistence
Circulatory system	Chest tightness or pain, palpitation, arrhythmia, myocarditis, post-exertional malaise	Autonomic dysfunction, virus persistence
Hematologic system	Thrombosis, autoimmune thrombocytopenic purpura	Immune dysregulation, coagulation dysfunction, vascular endothelium damages
Mental health and nervous systems	Dizziness, insomnia, hyposmia, hypogeusia, headache, brain fog, fatigue	Impact of pandemic, brain infection, neuroinflammation, autoimmune reaction
Digestive system	Abdominal pain, dyspnea, nausea, irritable bowel syndrome	Virus persistence, autonomic dysfunction, intestinal microbiome abnormality
Motor system	Fatigue, muscle or joint pain, post-exertional malaise	Autoimmune reaction, chronic inflammatory

Respiratory system

Long COVID is a disease involving multiple systems, and respiratory system is one of the most attack targets of SARS-CoV-2. The respiratory symptoms and signs are still relatively common and highly clinically concerned. In adults, common respiratory symptoms of COVID-19 include dyspnea (40–50%), chest tightness or pain (1–31%), and cough (1–30%) (3,6,28). Moreover, attributed to respiratory restriction and other reasons, exercise tolerance decreased by different proportions in different patient groups. Their quality of life and psychological assessment results also demonstrated they were influenced at different degrees (35,39). In a number of case reports about pulmonary function, the assessment of children cases after recovering from COVID-19 did not show a significant impact, different from the generally impaired pulmonary function of adults. The majority data showed no significant decrease compared with the normal population, and the slight decrease could not be attributed to long COVID (40,41). In another case report, a 3-month follow-up showed that 14% of children cases had abnormal pulmonary function and 30% had reduced diffusion capacity, and the degree was closely related to the severity during the time of illness (42). While these may not apply in all situations, these findings illustrated that the severity of primary COVID-19 does have an impact on prognosis and lung injury. In an imaging study of long COVID, lung computed tomography (CT) findings were closely associated with the primary disease and gradually improved after recovery, but the association between the findings and long-term respiratory symptoms is not clear (39). Additionally, clinical studies have found vagus nerve inflammation in adults following COVID-19 infection, which is correlated with cough and other respiratory symptoms of long COVID (43,44). However, there is a paucity of relevant studies investigating this phenomenon in children.

Circulatory system

Heart is another organ frequently involved in primary SARS-CoV-2 infection, and the heart function is closely related to the respiratory system. Cardiac involvement is also common. Common symptoms including chest tightness or pain (1–31%), palpitation and arrhythmia (6%) often accompany by motor limitations and shortness of breath (7,39). In the disease assessment of children, CT, X-ray and other imaging methods are not widely used when compared with adults, and they are usually not used in children without obvious symptoms, bringing difficulty in collection of relevant disease information and data. Studies on myocardial enzyme spectroscopy are also less common than those of adults. However, in adult studies, sequelae such as myocarditis, chronic heart failure and postural orthostatic tachycardia syndrome have been reported among patients who had recovered from acute infection (45,46), which also suggest the necessity of operating non-invasive examinations in children. In research assessing ventricular function, it was found that children may develop chronic left ventricular deformation and dysfunction, which may be related to chronic inflammation of myocardium (47). Another study speculated that the changes might be related

to the destruction of the myocardial mitochondria (48). Moreover, autonomic dysfunction may serve as a potential mechanism for circulatory system-related symptoms, including postural hypertension, fatigue discomfort, and syncope (32,49). The function of the autonomic nervous system is closely associated with the circulatory system (50), and several studies have indicated a potential association between primary COVID-19 infection and the development of autonomic nervous system disorders (51,52). Furthermore, in studies on long COVID, there has been evidence of autonomic nervous dysfunction contributing to associated clinical symptoms, which may have a strong genetic correlation in patients (53-55).

Hematologic system

The inflammatory cytokine storm caused by the acute phase of COVID-19 is a crucial factor contributing to the deterioration of condition even critical illness of patients during the early pandemic (56,57). And with the gradual analysis of the mechanism related to long COVID, it is found that the risk of thrombosis plays an important role in the progression of long COVID. In a prospective study, factor VIII levels were elevated in severely ill children, and the median D-dimer level was higher in patients with long COVID than control groups in different follow-up groups, but it was still within the normal range (27). However, children did not show significant changes in potential intrinsic thrombin, von Willebrand factor (vWF), peak thrombin and other indicators where adult patients' results elevated (58), which reflects that children's blood system is less affected. In another study, pulmonary perfusion was found abnormal and microthrombi were observed in peripheral blood (59). As for the mechanism of thrombosis, vascular endothelial injury caused by different pathway disorders was attributed to it, including VWF-ADAMTS-13 axis imbalance (60), interferon 1 (IFN-1) affecting mitochondrial function, and the body's pro-coagulant status (61).

Mental health and nervous systems

The SARS-CoV-2 pandemic has devastated people all over the world physically and psychologically, especially children who are not yet well developed physically and mentally. From this perspective, more attention should be paid. In the field of mental health, children manifest symptoms of depression, withdrawal, sleep disorder, brain fog, post-traumatic stress disorder (PTSD) and other symptoms (62,63), which are particularly implicated in behaviors such as lack of social interaction and movement and prolonged use of electronic devices during the pandemic. Among them, brain fog symptoms have attracted the attention of researchers. As a vital period of brain development, the influence related to virus infection is more serious and far-reaching under the age of 12, and the negative impact of brain fog symptoms on the intellectual development of school-age children may be accompanied lifelong (64). Meanwhile, psychiatric symptoms will also lead to other behavioral and physical abnormalities, such as obesity (65), which even have a further impact on the future of children, requiring active interventions from clinicians, teachers, families and society. In terms of nervous system, children with long COVID often manifested fatigue (2–87%), headache (7.5–66.7%) and hyposmia (1.7–2.2%) (66,67). Guido *et al.* found the phenomenon of fluctuations in symptoms (63).

As for the mechanism of occurrence of psychoneurotic symptoms and mental health impairment, several case studies of children have found that children with neuropathy-related symptoms of long COVID may have cerebral metabolism, which may be related to smell and taste decrease or neurocognitive problems (68-70). Ancona *et al.* found that gut-brain axis dysfunction in patients with COVID-19 was associated with neurological/psychiatric symptoms (71). In another case series, brain infection, neuroinflammation, autoimmune response, and environmental effects of the pandemic were proposed as possible pathogenic mechanisms (66). Among these factors, the impact of the pandemic on mental health problems stands out as particularly critical. Numerous studies have indicated that the COVID-19 pandemic may exert a significant influence on children's manifestations of abnormal mental states like anxiety and depression (62,72-74). Additionally, it may have an even more severe impact on children who already have existing mental illnesses (75,76).

Latest research in treatment of long COVID

There is no specific therapy for children with long COVID yet. At present, expectant treatment is carried out according to different clinical characteristics and related symptoms of patients. Exercise intolerance, fatigue and cardiopulmonary dysfunction exist in children with long COVID, which can be improved by exercise therapy. Ogonowska-

Slodownik *et al.* demonstrated that after 8 to 12 weeks of training in playing games and aerobic exercise, children's cardiopulmonary function measures such as forced vital capacity (FVC) and maximal oxygen uptake (VO_2max) improved (77). Dietary therapy is also a potential treatment. In adult clinical practices, vitamin, mineral and other nutrient supplements have certain benefits, which may be related to their functions of reducing inflammatory response and oxidative stress (78,79). In another study, lactoferrin was found to have a potential benefit in alleviating chronic gastrointestinal symptoms (80).

SARS-CoV-2 infection may cause the abnormal activation of mast cells, which promotes the inflammatory response *in vivo* and leads to allergic disease, so antihistamines have become another direction of clinical research (78). In the study of May *et al.*, it was found that the drug combination of levocetirizine and montelukast could effectively inhibit the inflammatory response of the body, and had a unique effect in the prevention and treatment of long COVID (81).

In terms of psychological treatment for children, corresponding solutions have been proposed in previous regional pandemic-diseases: using art and play therapy to help children rebuild healthy social relationships, and establishing local mental health centers to provide psychological counselling and communication services for children and adolescents. These measures have also been demonstrated to be effective treatments in a previous review (62).

Prevention of long COVID

At present, there are no specific strategies and guidelines for the prevention and treatment of long COVID. The following preventive measures have been proven effective in clinical practice according to relevant clinical tests. Vaccination can effectively reduce the rate of severe illness, which is conducive to the disease recovery of children with severe illness, and decrease but not eliminate the morbidity of long COVID additionally (11,13,14), however, the precise effect and specific mechanism have not been elucidated. According to the data from the relevant systematic review, which also suggest that the complete multi-dose vaccination of SARS-CoV-2 vaccine may be more effective in preventing long COVID (82). It is of the same importance to carry out etiological prevention according to the potential pathogenesis, and risk stratification should be carried out according to the potential risk factors so as to give corresponding treatment (61), such as reducing the occurrence of obesity and controlling the severity of the primary SARS-CoV-2 infection by dietary adjustment. Breastfeeding has a certain protection and prevention effect against long COVID in infants, however, no obvious association was found in children over 10 years old (83), which may be related to the antibodies and nutrients provided by breast milk for infants. Insufficient understanding of SARS-CoV-2, which is a vital factor leading to the mental symptoms of long COVID, and can lead to psychological changes such as excessive panic. Therefore, it may be one of the effective preventive measures to compile relevant popular science teaching materials for different ages to facilitate children to understand SARS-CoV-2 more clearly (62). A recent study of adults with long COVID published in the Lancet preprint found that early treatment with metformin was associated with a 42% relative decrease in the incidence of long COVID compared to exact-matching placebo, and treatment with metformin within 4 days of onset was associated with a 63% relative decrease (84). Currently, there is insufficient research regarding the use of metformin in children as a preventive measure for long COVID. The use of metformin in children should only be considered for those who are 10 years old and above, aligning with its established usage as a medication for diabetes. However, it is crucial that parents or guardians provide informed consent. Given that this study focuses on adults, there is a limited availability of clinical data for children, thereby making it difficult to endorse the routine use of metformin as a preventive drug for long COVID in pediatric patients.

Conclusions

Research on children's long COVID gradually increases and it is foreseeable that, alongside the greater depth of experiment on adults' long COVID developed, the long COVID study in pediatrics will continue to be improved and perfected. This review focuses on the latest research progress of long COVID in children around the world, including epidemiology, pathogenesis, clinical manifestations, treatment and prognosis, so as to provide advice for subsequent clinical research and diagnosis and treatment. However, we should point out that there still exist some deficiencies in this research field. The selection criteria of control group were different in different studies. Some studies selected patients with COVID-19 who did not show symptoms of COVID-19 as the control group,

while others selected patients without COVID-19 as the control group. In addition, the possibility of selection bias will increase due to the presence of asymptomatic infected persons. The variation in viral strains can result in different clinical manifestations, along with potential changes in pathogenicity and clinical characteristics. These factors can contribute to discrepancies between long COVID studies, particularly when comparing studies conducted at different times and in different regions, thereby increasing the difficulty of analysis. The variation in sample sizes among studies can introduce interference when conducting overall analyses. However, it is crucial to recognize and acknowledge the importance of these smaller sample sizes. Despite their limitations, these samples play a valuable role by addressing specific areas where data is lacking, such as in the case of immunodeficiency. Therefore, they are equally important and noteworthy for filling existing gaps in knowledge. The issue of recall bias is another concern to consider, as many of the studies conducted were retrospective in nature. The format of the studies, particularly in their early stages of the COVID-19 pandemic, primarily relied on questionnaires. However, it is important to note that this approach may introduce a potential selection bias. The degree of attention and participation in completing the questionnaires may vary among different groups of people. Those experiencing long COVID symptoms may be more inclined to attach greater importance to the questionnaires compared to individuals without symptoms. This discrepancy in engagement with the questionnaires can influence the accuracy and representation of the data collected. Limited epidemiological data is available on children, and existing studies often suffer from small sample sizes that are not statistically significant. Furthermore, it is important to acknowledge that the incidence and impact of long COVID in adults cannot be used to represent the situation in children accurately. Therefore, there is a clear need for large-scale clinical studies dedicated to children in order to obtain comprehensive insights into long COVID specifically in pediatric populations.

We suggest that further studies in long COVID treatment should be carried out with being classified according to specific symptoms to make progress in the treatment of different types of patients, and finally facilitate their functional recovery and improve prognosis. Moreover, further research should also be carried out on the pathogenesis, which can provide support for analysis of long COVID and other atypical coronavirus-related pneumonia by exploring susceptible population's characteristics, tissue biopsy, blood biochemical and immunological governments should also make early intervention by assessing risk factors that can be easily tested to reduce potential losses and more importantly, to protect those susceptible children and adolescents.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-472/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-472/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-472/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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Cite this article as: Zhang J, Kuang T, Liu X. Advances in researches on long coronavirus disease in children: a narrative review. Transl Pediatr 2024;13(2):318-328. doi: 10.21037/tp-23-472