

Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19

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Abstract

Aim: Persistent symptoms in adults after COVID-19 are emerging and the term long COVID is increasingly appearing in the literature. However, paediatric data are scarce.

Methods: This paper contains a case report of five Swedish children and the long-term symptoms reported by their parents. It also includes a systematic literature review of the MEDLINE, EMBASE and Web of Science databases and the medRxiv/bioRxiv pre-print servers up to 2 November 2020.

Results: The five children with potential long COVID had a median age of 12 years (range 9–15) and four were girls. They had symptoms for 6–8 months after their clinical diagnoses of COVID-19. None were hospitalised at diagnosis, but one was later admitted for peri-myocarditis. All five children had fatigue, dyspnoea, heart palpitations or chest pain, and four had headaches, difficulties concentrating, muscle weakness, dizziness and sore throats. Some had improved after 6–8 months, but they all suffered from fatigue and none had fully returned to school. The systematic review identified 179 publications and 19 of these were deemed relevant and read in detail. None contained any information on long COVID in children.

Conclusion: Children may experience similar long COVID symptoms to adults and females may be more affected.

KEYWORDS

coronavirus, fatigue, heart problems, long COVID, pandemic, school attendance

1 | INTRODUCTION

The clinical spectrum of COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),¹ ranges from asymptomatic to severe respiratory symptoms,² extra-pulmonary manifestations and death. The disease course seems milder in

children,³ but a small proportion develop hyperinflammation.⁴ This has been described using a number of terms and the most common is probably multi-inflammatory syndrome in children (MIS-C).

Increasing attention has been paid to the long-term effects of COVID-19 and the commonly used term for this is long COVID. While data are scarce, some suggest that a substantial proportion

Abbreviations: COVID-19, coronavirus disease 2019; Long COVID, long-term effects of COVID-19; MIS-C, multi-inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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of individuals with COVID-19 have the persistent symptoms that are characteristic of long COVID.⁵ Symptoms in adults include fatigue, headache, dyspnoea, cognitive impairment, depression, skin rashes and gastrointestinal complaints. While there is a growing body of literature on long COVID in adults,⁵⁻⁷ the data on children are scarce.

The aim of this paper was to describe five children with long COVID, based on parental reports, and complement those cases with a systematic literature review of long COVID.

2 | METHODS

2.1 | Case reports

In late October 2020, I was one of a number of physicians and healthcare personnel who were contacted by the parents of three children who had met on an Internet-based social media forum after their children were diagnosed with COVID-19. They had noted our interest in COVID-19 and were keen to raise awareness of the ongoing symptoms that their children were experiencing after contracting the virus. When I expressed interest in their reports, a further two parents contacted me. My contact with them was limited to clarifying their parental reports, obtaining written, informed consent for their children's data to be used in this paper and assuring them that any data that were used would be anonymised. The different areas of data gathered were decided after hearing the histories of the families. Separate consent was obtained from children aged 12 years or more.

In this Swedish case report, we defined long COVID as persistent symptoms that lasted for 2 months or more, as this corresponded to the mean duration reported by Carfi et al.'s⁷ follow-up of 143 adults, which found that 87% had persistent symptoms after COVID-19. All the data are based on parental reports of the five children.

2.2 | Systematic literature search

A librarian at the Karolinska Institutet University Library, Stockholm, Sweden, performed a systematic literature review of the MEDLINE, EMBASE and Web of Science databases on 2 November 2020 to identify papers on long COVID in children. In addition, the librarian also performed a search of medical papers filed on medRxiv/bioRxiv up to the same date. This is a pre-print database for biology papers, which is operated by the Cold Spring Harbor Laboratory, a private research and educational institution in New York, USA.

We used the same search terms for COVID-19 and SARS-CoV-2 and children as we did in our two previous systematic reviews of COVID-19.^{8,9} However, we also added following terms, and variants of these terms, to specifically catch publications that discussed long COVID: chronic, post-acute, post-COVID, long COVID, long haulers, persistent, sequelae or complications. Details of the searches can be found in Appendix S1.

Key notes

- This paper presents a case report of five Swedish children aged 9–15 and the parental reported symptoms they experienced more than 2 months after clinical diagnoses of COVID-19.
- All had fatigue, dyspnoea, heart palpitations or chest pain, four had headaches, difficulties concentrating, muscle weakness, dizziness and sore throats and females appeared to be over represented.
- The accompanying systematic review did not reveal any data on long COVID in children.

After the duplicates were removed, the search identified 179 papers: 82 in MEDLINE, 20 in EMBASE, 58 in Web of Science and 19 in medRxiv/bioRxiv. The author read 19 in detail after screening the titles and abstracts. Of these, 11 were from MEDLINE,¹⁰⁻²⁰ two from EMBASE,^{21,22} five from Web of Science²³⁻²⁷ and one from medRxiv/bioRxiv.²⁸ There was no pre-specified protocol prior to the review.

3 | RESULTS

3.1 | Case reports

Of the five children with potential long COVID, four were girls and their median age was 12 years (range 9–15). The children had experienced symptoms for between 6 and 8 months. All had been diagnosed with COVID-19 by their physician. None of the children had positive SARS-CoV-2 polymerase chain reactions, but the tests had been obtained more than 1.5 months after the onset of COVID-19. SARS-CoV-2 antibody testing had been carried out on four of the five children, but all the tests were negative. It was not necessary for any of the children to be admitted to hospital at the onset of COVID-19. The clinical details of the children, based on parental reports, are presented in Table 1. Only one child had comorbidities before developing COVID-19 and that was a 12-year-old female with asthma, allergies and mild autism spectrum disorder.

The most common symptoms 2 months after the onset of COVID-19 were fatigue, dyspnoea and heart palpitations or chest pain. These were seen in all five of the children. In addition, four of the five children complained of headaches, difficulties concentrating, muscle weakness, dizziness and a sore throat.

The parents reported that three of the children experienced abdominal pain, memory loss, depression and skin rashes and muscle pain. Less common symptoms, experienced by two children, were remitting fever, sleep disorders, joint pain, diarrhoea and vomiting and hyperaesthesia. A number of symptoms were each reported

TABLE 1 Background details and clinical data reported by the parents of five children with long-term effects of COVID-19

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex, age	Female, 13 years	Female, 12 years	Male, 11 years	Female, 9 years	Female, 15 years
Earlier comorbidities	-	Asthma, allergies and mild autism spectrum disorder (normal schooling)	-	-	-
Symptoms	6.5 months	7.0 months	6.0 months	8.0 months	8.0 months
Other contacts at COVID-19 onset	Other family members sick	Father fell sick 10 days before child	Mother and patient's friend fell sick at the same time	Mothers and two siblings were also ill	Child and several travel companions sick during holiday abroad
Initial COVID-19	Fever, abdominal pain, upper respiratory symptoms, extreme fatigue. Body felt very heavy. Deep cough. Lost taste and smell after 2 weeks	High fever with abdominal pain and headache. Lost taste and smell. Dyspnoea. Extreme fatigue. Dizziness	Headache and sore throat. Thirsty for first 2 weeks. Abdominal pain, diarrhoea, nausea and anorexia. Lost taste and smell	Fever, diarrhoea, headache, abdominal pain, nausea and dyspnoea for several weeks	High fever, headache, dyspnoea and chest pain. Very tired
Long COVID- (after 2 months)	Stayed in bed for 3 months (mid-April to August), except to visit shower and toilet. Developed skin rash after two months and severe pain in her arms and hyperaesthesia after 4 months	Sick for 11 weeks. Depressed, angry. Lots of abdominal pain. Repetitive behaviour. Worsening autism spectrum disorder. Increased tics. Developed peri-myocarditis. Admitted to hospital for 3 days due to this cardiac complication. Recent exercise ECG normal	Fluctuating symptoms. Distorted smell and taste. Anorexia and nausea. Abdominal pain, especially in evenings. Constipated. Fatigued. Usually stayed in bed until noon. Sub febrile (37.8 C). Could not walk > 100 metres. Swollen lymph nodes. Chest pain. Skin rash. Hyperaesthesia, but numbness in some fingers. Joint pain and back pain. Dizziness. High pulse, even with limited physical exertion	Symptoms escalated 4–5 months after disease onset, with chest pain, sensory impairment. Fever, nausea and abdominal pain. Extreme fatigue. No strength to speak. Dyspnoea. Could not climb stairs. Felt legs and other body had 'died'	Slept for 16–18 h per day. Dyspnoea, chest pain, dizziness. Cognitive impairment

(Continues)

TABLE 1 (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Current status	<p>Extreme fatigue. Complains body is very heavy. Remitting fever and high pulse. Difficulties breathing when she moves. Pain in arms have gone, but fatigue worsened in late October and was in bed for 1.5 weeks. So fatigued that she communicates with her hands rather than speaking.</p>	<p>Fatigued. Sleeps well, but has started to take melatonin. Depressed, and medicates with sertraline. Difficulties with concentration. Has more tics than usual when stressed, but autism spectrum disorder has returned to pre-COVID-19 status. Lot of abdominal pain. Sometimes headache</p>	<p>Symptoms have improved, but patient continues to have fatigue. Low tolerance to exercise and frequently gets abdominal pain. ECG, exercise ECG and heart ultrasound OK. Physician suspects post-myocarditis. Will see child psychologist</p>	<p>Symptoms remain. Tired. Has undergone testing with ECG, heart ultrasound, blood tests, spirometry, and throat culture. All negative</p>	<p>Brain fog. Concentration difficulties. Memory loss. Weight loss. Not hungry. Has stopped exercising at elite level. Negative test for lung thromboembolism. Seeing physiotherapist, and will see psychologist</p>
School attendance	<p>Part-time attendance. Cannot use the stairs, but has an elevator at her school. Her parents drive her to school</p>	<p>Distance learning. Attends roughly 50% of the lectures from home</p>	<p>Part-time attendance. Attends school on 3 days: 2 days for 2 h and 1 day for 1 h. Distance learning from home on other 2 days</p>	<p>Attends school 50% of the time</p>	<p>No school for first 3 months. Just started upper secondary school, mainly through distance learning^a. Attends when feels OK</p>
Support/how to improve the child's complaints	<p>Parents focus on giving her food and drink and making her take her pain medication</p>	<p>Parents have removed all demands. Patient cannot cope with them</p>	<p>Needs to rest. Parents focus on the patient eating and drinking</p>	<p>Improves if sleeps well. Rests during day. Parents think vitamin C may be helping</p>	<p>Takes dextrose to increase energy levels. Has begun taking dietary supplements</p>

Note: For additional information on symptoms, see main text.

Abbreviation: ECG, electrocardiogram.

^aIn Sweden, some upper secondary schools have continued with part-time distance learning during autumn 2020.

by one child after 2 months, and they were persistent deranged smell and taste, poor appetite, a chronic cough and numbness.

Some of the children had improved after experiencing symptoms for 6–8 months, but all of them still suffered from fatigue and none of them had been able to return to school full time. Four reported daily problems of some kind while a fifth was reported to have 'good and bad days'.

The parents stated that two of the children had undergone cardiac examinations and two had seen, or were scheduled to see, a psychologist. The girl with prior comorbidities was hospitalised for 3 days for peri-myocarditis after being diagnosed with COVID-19.

Several parents also reported that they or the children's siblings also had longstanding issues as a result of COVID-19. These included the mothers and two siblings of patient four (Table 1).

One parent noted that it was general knowledge on Internet-based social forums for long COVID patients that mothers and their daughters often had long COVID simultaneously.

3.2 | Systematic literature review

Most of the 19 publications read in detail concerned general^{16,24} or specific^{15,25,26} medical aspects of COVID-19, but they did not describe any children with long COVID. Other publications concerned how COVID-19 may influence different aspects of children's lives.¹¹

In a systematic review, Ahmed et al.¹⁰ described the clinical characteristics of 662 children with MIS-C, but reported no long-term consequences other than MIS-C. It was unclear if any of the MIS-C cases that the authors described occurred more than 2 months after the onset of COVID-19. Other studies focused on individual cohorts of children with MIS-C or COVID-19 and the need for intensive care,¹³ hospital admission²⁷ or other aspects of MIS-C or COVID-19.²³

In a brief report, Denina et al.¹⁴ followed up 28 children admitted to hospital with COVID-19. On average, children were followed up for an average of 35 days after discharge, but the authors did not state the average time lapse between hospital admission and follow-up. After they were discharged, none of the children demonstrated any clinical or laboratory abnormalities. The authors noted that no sequelae remained 4 months after discharge.¹⁴

Finally, the other studies identified in our review concerned COVID-19 in adults.^{12,17,20} Radmard et al.²¹ discussed neurological complications after COVID-19 and presented data on 33 patients. There was only one paediatric patient under the age of 18 and that individual was 17 years of age. No detailed follow-up data were provided. Although it was not explicitly stated, the median age of the 48 patients in the pre-print study by Savarraj et al.²⁸ was 50 years and children were not mentioned. Yasin et al. reviewed respiratory symptoms and x-ray results²² in subjects with a mean age of 42 years, which included an unspecified number of children aged 12–17. It is unclear if any of the documented abnormalities at more than 15 days persisted for two or more months and were seen in children.

I was unable to access a case report of four adolescents with skin lesions, 2 weeks after the occurrence of a flu-like syndrome.¹⁸ The patients tested positive for SARS-CoV-2 antibodies, but it was not clear from the abstract if these potential cutaneous manifestations persisted for more than 2 months.

4 | DISCUSSION

This paper presents detailed parent reported data on five children with potential long COVID that lasted for more than 2 months, which was the mean duration reported by Carfi et al.'s follow-up of adults with long COVID.⁷ In fact, the children all had symptoms for at least 6 months. The children who were between 9 and 15 years of age had substantial difficulties many months after the onset of COVID-19 and this was reflected by their poor school attendance.

In Sweden, preschools and elementary schools were kept open during the first wave of the pandemic in spring 2020.²⁹ Early COVID-19 reports suggested that children had milder disease symptoms than adult and a better prognosis. During late spring 2020, reports started to emerge of a Kawasaki-like hyperinflammation.⁴ Widely known as MIS-C,¹⁰ this often occurs in children who test positive for antibodies and it is possible that it appears after a diagnosis of COVID-19 infection, rather than during the acute phase of the disease. However, my impression is that MIS-C remains an uncommon complication in children with COVID-19.

Of the five children in our case report, four were female and that ratio of 4:1 was also reported by a French study. The hospital saw some 30 patients weeks with persistent symptoms and noted that many were females around 40 years of age.³⁰ Since the data were collected on the five children in the case report, more parents have contacted the author and the majority of those had daughters who seems to have long COVID.

This case report yields no clues about the frequency of long COVID in children. In adults, a review by Greenhalgh et al.⁵ suggested that up to 1 in 10 adults suffered prolonged symptoms up to 3 weeks after COVID-19 was diagnosed. Clearly, future studies should look into the prevalence of long-term complications from COVID-19 in children. While earlier risk factors for prolonged COVID-19 have been reported in adults,⁵ none of the papers covered by our systematic review discussed predisposing factors. Four of the five children in the case report had no comorbidities prior to COVID-19. The fifth had asthma, allergies and autism spectrum disorder. The fact that long COVID may occur in healthy children is consistent with data in adults.³⁰ None of the children was admitted to hospital at the onset of COVID-19, but the girl with prior comorbidities did spend 3 days in hospital with peri-myocarditis 3 months after she was diagnosed with COVID-19. In addition, many adults with long COVID have had mild initial disease.

Carfi et al.⁷ described the 143 adults admitted to hospital for COVID-19, who were followed up at an average of 60 days after disease onset, in a research letter to *JAMA*. Of these more than 87%

had at least one persistent symptom and most frequent were fatigue, dyspnoea, joint pain and chest pain.

All five children in our study reported fatigue and dyspnoea, but joint pain and chest pain were also common. Other symptoms ranged from neurological complaints to skin rashes, sleep disorders, depression, muscle pain and remitting fever. However, fatigue seems to stand out as the predominant symptom and it persisted at end of follow-up in all five children. In a paper by Rubin,⁶ unpublished data from 1500 long COVID adult patients showed fatigue to be the most frequent persisting symptom. Long-term fatigue is not uncommon after other viral infections.³¹ When Lam et al.³² followed up 369 severe acute respiratory syndrome survivors 4 years after they developed the disease in the first decade of this century, they found that more than 40% reported fatigue. Although it is often overlooked, narcolepsy, which is characterised by extreme fatigue, increased substantially among unvaccinated Swedish children during the H1N1 influenza pandemic of 2009–2010. It is likely that this reflected increased exposure to the influenza virus.³³

All five children in our case report also reported dyspnoea, which Carfi et al.⁷ saw in 43% of their adults with long COVID. Other frequent symptoms, reported by one in five adults in that study, were heart palpitations and chest pain.⁷ Data now suggest that COVID-19 may have cardiovascular consequences in both adults³⁴ and children^{10,15,25} and that chest pain is common in adults.^{5,7} It is notable that several of the children in our case report had palpitations, with a high pulse rate on exertion and an inability to perform physical activity. In addition, the only child who was hospitalised in our case report had peri-myocarditis.

The children in our case report also experienced gastrointestinal, neurological and cognitive symptoms, which were all consistent with the extra-pulmonary manifestations reported in acute COVID-19 patients.^{5,35}

It is interesting that sometimes several people in the same family as the children in this report had long COVID. This suggests that shared genetic or environmental traits might predispose some individuals to long COVID.

4.1 | Clinical implications

Most children with COVID-19 show few symptoms and have a mild form of the disease.⁸ However, it has become clear that a small proportion develop MIS-C¹⁰ and some may even need intensive care.¹³ Although the current systematic review found no earlier reports of long COVID, the five children aged 9–15 years in our case report testify to the existence of long-term complications from COVID-19 in children. While I was writing this case report, I became aware of even more children with long COVID, as more parents contacted me, but these were not included in this case report.

This case report and review raise a number of questions and point to future research needs. More research is needed into the prevalence and prognosis of long COVID in children. Affected children need relevant follow-up visits that consider child-specific aspects and the strategy outlined by Greenhalgh et al.⁵ may be a useful

starting point. The fact that the children in the case report had still not returned fully to school at the time of writing, despite Swedish schools being open for children up to the age of 16 throughout the pandemic⁸ adds to the seriousness of the matter.

Swedish healthcare³⁶ should follow-up children with long COVID and their rehabilitation needs should be assessed.

4.2 | Strengths and limitations

This study had some strengths and limitations. One strength was the systematic search of a number of highly respected medical databases, including the medRxiv/bioRxiv pre-print servers. Despite our extensive search, I failed to identify any report that specifically described long COVID in children.

The limitations of our review include the lack of granular data on blood tests and other investigations to rule out differential diagnoses. Although I cannot rule out that the children had MIS-C, or even Kawasaki disease, the long symptom duration argues against MIS-C and Kawasaki disease as the explanation for the symptoms of these children. The data in the case reports were reported by the parents of the five children. Given the clinical spectrum of long COVID in the five patients, full haematology, electrolytes, cardiac markers and inflammatory markers would have been useful. Tests to rule out differential diagnoses, such as other inflammatory or autoimmune conditions, would also have been useful. Several, but not all of the patients in our case report, had undergone heart examinations. Still it would have been preferable to include detailed echocardiography data on all five children in this review.

It is possible that the children in this case report have more severe long COVID than the average child. The fact that their parents reached out to the medical community may also signal that their children had a severe form of long COVID.

Although all of the five children had been diagnosed with COVID-19 by their respective physicians, none of them had been tested positive for COVID-19 at the time of their diagnosis. It worth noting that it has been suggested that a positive test is not required for a diagnosis of long COVID.⁵ That fact that the polymerase chain reaction tests for SARS-CoV-2 were negative is not surprising, since they were not obtained during the acute phase of COVID-19. Sweden suffered from a lack of testing equipment during spring 2020 when these children fell sick,²⁹ and testing was primarily targeted at hospital inpatients and healthcare personnel. Still I acknowledge that other explanations for the ongoing symptoms cannot be fully ruled out. None of the children were admitted to hospital during spring 2020, but patient two was later admitted for peri-myocarditis.

5 | CONCLUSION

This case report on five children and the accompanying systematic review add to the growing evidence that long COVID may potentially

occur also in children and that it can be very debilitating and lead to long school absences. The symptoms that were reported by the children's parents were similar to those reported by studies of adults with long COVID. The case report and the growing number of parents that have made contact suggest that females may be more prone to developing long COVID, as seen in adult studies.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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