Children and long-COVID: Do they go together?

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The notion that some patients have residual symptoms for months or even years following a viral infection is not new (1). The term *myalgic encephalomyelitis* first appeared in publications in 1956 (2). The entity was renamed *chronic fatigue syndrome* following an outbreak in Incline Village, Nevada in 1984. A consistent link to any specific virus is yet to be identified and there are no uniform abnormalities on standard laboratory or other investigations. There is some overlap with fibromyalgia with the latter being characterized by debilitating muscle pain.

Persistent symptoms have now been linked to SARS-CoV-2 infection. This is not surprising. Roughly half of Canadians have been infected by August 2022, presumably constituting the largest outbreak of a specific viral infection ever to occur in this country. Due to widespread availability of laboratory and home testing for COVID-19, for the first time ever, the general public now know if they have been infected with a specific respiratory virus, leading them to potentially attribute subsequent symptoms, deemed long-COVID, to that documented infection.

There is a great need to study consistent symptoms and outcomes to better understand long-COVID (3). It is vital that the syndrome is not confused with rare but well-recognized sequelae of viral respiratory tract infections such as pulmonary fibrosis. In October 2021, the World Health Organization (WHO) released the following Delphi consensus definition:

> Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children.

The WHO document provides definitions from nine other organizations (4). Four definitions list a minimum duration of symptoms post-COVID-19, ranging from 4 to 12 weeks.

The incidence of long-COVID in children is difficult to establish given that diagnostic criteria cannot be validated as there are no pathognomonic features. The incidence of presumed long-COVID appears to be lower in children than in

Table 1: Methodology of studies that compared persistent symptoms in children infected with SARS-CoV-2 to controls

Country (Reference)	Methodology	Cases	Controls (SARS-CoV-2 negative or never tested)	Proof of infection in cases	Time between COVID-19 diagnosis and follow-up	Data collected from cases and controls
Published studies						
Denmark (6)	Parental online survey	All children in Denmark who tested positive up to Jul 12, 2021, of whom 29% participated	Matched 1:4 for sex and age, identified from civil registry so many never tested	PCR-positive	2 months	Asked whether any of 23 symptoms had persisted for 2 months
8 countries (7)	Parental telephone or email survey	Children from 36 EDs seen Mar 7, 2020–Jan 20, 2021, of whom 80% who were approached participated	Tested in same EDs, matched for hospitalization status, country, and recruitment date	PCR-positive	90–120 days	Asked open-ended questions about new or persistent symptoms
Latvia (8)	Parental or patient face-to-face survey	Infected Jul 2020–Apr 2021, recruited by advertising (median 10 years old)	Had another respiratory illness, recruited by family physicians (median 2 years old)	PCR-positive or seropositive	1–6 months (median 73 days for cases and 69 days for controls)	Asked whether any of 22 symptoms were persistent
Switzerland (9)	Parental online survey	Children in 55 schools who consented to having serology done who were seropositive of whom 54% of potential cases and controls combined participated	Seronegative children in same schools	Seropositive	Timing of infection not known	Asked about symptoms that persisted for >12 weeks Jun 2020–Apr 2021
England (10)	Parental online survey	Children 11–17 who tested positive Jan 1–Mar 31, 2021, of whom 13% participated	Tested negative same dates, matched for age, sex, geographical region	PCR-positive	3 months	Asked whether 21 symptoms were present 3 months prior and on the date they completed the survey
UK (11)	Parental online survey	Children whose parents entered them in an app when they were tested of whom approximately 50% logged symptoms	Children whose parents entered them in the app who tested negative match by age, gender and week of testing	PCR-positive (self-reported)	28 days	Asked about open-ended symptoms daily and included ones that persisted for 28 days

(*Continued*)

Table 1: Continued

Country (Reference)	Methodology	Cases	Controls (SARS-CoV-2 negative or never tested)	Proof of infection in cases	Time between COVID-19 diagnosis and follow-up	Data collected from cases and controls
England (12)	Parental online or paper survey	Random selection of those positive in one week Jan 2021 of whom 21% completed follow-up	Tested negative in the same week of whom 10% completed follow-up	PCR-positive	Minimum 1 month	Asked whether any of 64 symptoms occurred at least 5 times in the month prior
Denmark (13)	Patient or parental online survey	All children in Denmark who tested positive up to Mar 19, 2021, of whom 44.9% participated	Approached parents of children who attended daycare or public school of whom 21.3% participated	PCR-positive or seropositive	Weeks to months after infection (one-time survey)	Asked whether any of 15 symptoms had persisted minimum 4 weeks
United States (14)	Billing claims	Children with evidence for COVID-19 up to Jan 31, 2022	Matched 1:3 based on age, sex, and month of case	Positive SARS-CoV-2 test or COVID-19 billing code	60–365 days depending on when case occurred	Billing claims for 9 symptoms and 15 conditions
7 countries (15)	Diagnostic codes in electronic health research networks up to Apr 13, 2022	Children with COVID-19 up to Dec 31, 2021	Propensity score matched 1:1 to children with another respiratory infection	ICD10 codes for 'COVID-19, virus identified'	Up to 813 days depending on when case occurred	14 neurological and psychiatric diagnoses
Preprints						
UK and Wales (16)	Weekly household online surveys	Those who self-reported infection Jun 2020–Mar 2021	Those who completed weekly surveys and did not self-report infection	PCR-positive or seropositive	Minimum 4 weeks	Asked open ended questions about any persistent symptoms
Germany (17)	Patient survey (presumably online)	Students in 14 schools who had serology done and were seropositive	Students in same schools who were seronegative	Seropositive	Timing of infection not known	Asked about 7 symptoms and 5 moods Mar–Apr2021
Germany (18)	Billing claims	Children who tested positive up to Jun 2020	Matched 1:5 based on sex, age, and propensity score matching on prevalent medical conditions	PCR-positive or seropositive	Minimum 3 months	Billing claims for 96 outcomes in 13 symptom complexes

ED = Emergency department; PCR = Polymerase chain reaction; UK = United Kingdom

Table 2: Comparison of persistent symptoms in children infected with SARS-CoV-2 to controls

Country (Reference)	Age group	Cases with new symptoms at follow-up	Controls with new symptoms at follow-up	Absolute difference	Odds ratio (95% CI); *p*-value or other comparisons
Published studies					
Denmark (6)	0–3 y	478/1,194 (40.0%)	1,049/3,855 (27.2%)	12.8%	1.78 (1.55–2.04); *p* <0.0001
	4–11 y	1,912/5,023 (38.1%)	6,189/18,372 (33.7%)	4.4%	1.23 (1.15–1.31); *p* <0.0001
	12–14 y	1,313/2,857 (46.0%)	4,454/10,789 (41.3%)	4.7%	1.21 (1.11–1.32); *p* <0.0001
8 countries (7)	0–18 y (inpatients)	40/391 (10.2%)	19/380 (5.0%)	5.2%	
	0–18 y (outpatients)	55/1,295 (4.2%)	35/1,321 (2.7%)	1.6%	
	0–18 y (all patients)				1.63 (1.14–2.35)
Latvia (8)	1 mo to18 y	152/217 (70%)	32/129 (25%)	45%	*p* <0.0001
Switzerland (9)	6–16 y	4/109 (2%)	28/1,246 (4%)	2.0%	NR
England (10)	11–17 y: 3 or more symptoms at follow-up	936/3,065 (30.5%)	603/3,739 (16.1%)	14.4%	
	11–17 y: any symptoms at follow-up	2,038/3,065 (66.5%)	1,993/3,739 (53.3%)	13.2%	*p* <0.0001
UK (11)	5–17 y	77/1,734 (4.4%)*	15/1,734 (0.9%)	3.5%	*p* <0·0001
England (12)	2–16 y	21/320 (6.7%)	6/154 (4.2%)	2.5%	*p* = 0.24
Denmark (13)	0–5 y	439/2,979 (14.8%)	1,201/6,832 (17.6%)	–2.8%	*p* = 0.001
	6–17 y	3,374/12,065 (28.0%)	2,245/8,248 (27.2%)	0.8%	*p* = 0.02
United States (14)	0–17 y	*N* = 781,419	*N* = 2,344,257		Increased incidence of 5 symptoms and 6 conditions, decreased incidence of 1 symptom and 3 conditions and no change for 3 symptoms and 6 conditions
7 countries (15)	0–17 y	36,592/185,748 (19.7%)	39,193/185,748 (21.1%)	–1.4%	*p* = 0.29
Preprints					
UK and Wales (16)	0–17 y	8/174 (4.6%)	72/4504 (1.6%)	3.0%	2.48 (1.00–6.13)
Germany (17)	Grade 8–12	*N* = 188	*N* = 1365		No difference in cases versus controls for any of the 7 symptoms and 5 moods
Germany (18)	Children/ adolescents	437/1000 patient-years	336/1000 patient-years		IRR = 1.33 (1.31–1.34)

** 25/1,379 cases (1.8%) had symptoms at 56 days, but data are not reported for controls*
NR = Not reported; IRR = Incidence rate ratio; UK = United Kingdom

adults. A study from Russia reported residual symptoms that met the WHO definition in about 20% of 360 children 6 months post-admission versus 50% of 1,013 adults. At 12 months, 10% of children and 34% of adults had residual symptoms (5).

Table 1 shows the methodology of 13 pediatric studies that compared new-onset symptoms in children with SARS-CoV-2 infection to a control group (6–18). Table 2 shows the results of this comparison. All but three studies (12,15,17) report increased symptoms in cases versus controls in at least one age group. However, one study that reported such a difference reported higher quality-of-life scores related to emotional and social functioning in 12- to 14-year-old cases than in controls (6).

There are major limitations to these studies. Not all studies differentiated between persistent symptoms and symptoms present on the day of follow-up. Respondents were only potentially blinded to infection status in the studies that defined infection as seropositivity; even in those studies, some patients or their parents would have known when they were infected. Three studies reported diagnostic or billing claims (14,15,18) which may be more objective then self-reported or parent-reported symptoms. However, some children may not receive conventional medical care for persistent symptoms; perhaps those diagnosed with COVID-19 were more likely to receive care than controls. Parents reported symptoms if children were too young to do so, which is fraught with error. It might be difficult for parents and patients to remember whether symptoms pre-dated COVID-19 or to determine whether symptoms were related to another medical condition, a co-infection, or a subsequent infection. Participation rates were low for some studies; it seems possible that those with persistent symptoms, that they or their parents attributed to COVID-19, would be more likely to participate. Most studies did not control for chronic medical problems. Only one study controlled for inpatient versus outpatient status (7) and none controlled for severity of illness. It seems likely that at least some controls had unrecognized SARS-CoV-2 infections during the study period. None of the studies compared children with COVID-19 to those with another specific viral infection, although one used controls with a presumed non-SARS-CoV-2 infection (8). All but two studies predated circulation of the Omicron variant (14,15).

A further limitation is that symptoms are by nature subjective. Objective measurements were performed on 158 adults reporting persistent symptoms in a study from Sweden. Although extremity weakness was reported by 28% of patients, it could only be corroborated in 10%; 48% reported cognitive symptoms, but this could be documented in only 3% (19).

There are no validated risk factors for long-COVID in children or in adults. Risk factors were analyzed in only one of the studies in Tables 1 and 2 and included hospitalization for more than 48 hours, more that four symptoms at presentation, and being 14 years old or older versus less than 1 year old (6). A study of children hospitalized in Poland for COVID-19 found that symptoms beyond 12 weeks post-COVID-19 were more common in the 77 immunocompetent hosts than in the 70 immunocompromised hosts (35% versus 11%; $p = 0.01$), potentially because the latter were more likely to be admitted with mild disease or manifest less inflammation (20).

It is not clear to what degree persistent symptoms stem from the SARS-CoV-2 infection itself, the immune response to that infection, reactivation of latent herpes viruses such as Epstein-Barr, debilitation from severe COVID-19, mental health problems stemming from the infection or fear of sequelae, versus unrelated conditions that started about the time of infection. The biologic plausibility of the virus or the immune response to the virus causing persistent effects is yet unknown though some mechanisms have been theorized. These include cell destruction from proinflammatory cytokines, entry of virus into multiple organs via ACE2 receptors, immune cell hyperactivation, direct cell entry of neurological and muscle cells, hypercoagulation states and endothelial injury, but none have yet been proven. Laboratory or biochemical abnormalities do not correlate with symptoms (21). SARS-CoV-2 replication more than 2 months following disease onset seems to occur almost exclusively in immunocompromised hosts. One study reported differences in systolic blood pressure, left ventricular ejection fraction, relative wall thickness, and tricuspid annular plane systolic excursion in 121 children minimum 1-month post-COVID-19 when compared to 95 age and sex matched controls (22), but this is of uncertain clinical significance. There were no differences in pulmonary function tests in 73 children tested mean 2.6 months post-COVID-19 versus 45 controls (23). An adult study with baseline and follow-up MRI results for 401 cases with SARS-CoV-2 infection and 385 controls described

> (1) a greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus; (2) greater changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex; and (3) a greater reduction in global brain size in the SARS-CoV-2 cases than controls. (24 p697 [Abst])

They also reported poorer scores on two cognitive tests in cases versus controls. They do not discuss correlation with persistent symptoms.

We are not aware of any published studies of interventions for children with presumed long-COVID. However, ClinicalTrials.gov lists three trials involving three interventions: resistance exercise, the antioxidant mitoquinone, and

a rehabilitation robot (only for those who were ventilated), respectively.

Ideally, a prospective study with routine weekly or biweekly testing of a large sample size of children of all ages for SARS-CoV-2 and other viral infections, blinding of test results when practical, and weekly recording of symptoms to establish the incidence and natural history of SARS-CoV-2 infection and to determine how it varies from other respiratory viral infections should be undertaken. A recent study from Ontario reported that the novel blood biomarkers ANG-1 and P-SEL had high sensitivity and specificity for long-COVID in adults (25). Pending verification of those results in another centre, children with possible long-COVID deserve supportive care, but there is no evidence that they will benefit from specific investigations or therapy.

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