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Pediatric long-COVID: An overlooked phenomenon?

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Abstract

Background: Long-COVID is a well-documented multisystem disease in adults. Far less is known about long-term sequelae of COVID in children. Here, we report on the occurrence of long-COVID in Dutch children.

Patients and Methods: We conducted a national survey asking Dutch pediatricians to share their experiences on long-COVID in children. We furthermore describe a case series of six children with long-COVID to explore the clinical features in greater detail.

Results: With a response rate of 78% of Dutch pediatric departments, we identified 89 children, aged 2–18 years, suspected of long-COVID with various complaints. Of these children, 36% experienced severe limitations in daily function. The most common complaints were fatigue, dyspnea, and concentration difficulties with 87%, 55%, and 45% respectively. Our case series emphasizes the nonspecific and broad clinical manifestations seen in post-COVID complaints.

Conclusion: Our study shows that long-COVID is also present in the pediatric population. The main symptoms resemble those previously described in adults. This novel condition demands a multidisciplinary approach with international awareness and consensus to aid early detection and effective management.

KEYWORDS

infections, pneumonia, TB, viral

1 | INTRODUCTION

The post-acute sequelae of COVID-19, now recognized as long-COVID, post-COVID-19 syndrome, or post-acute sequelae of SARS-CoV-2 (PASC), have been well documented as a multisystem disease in adults. It is defined by the signs and symptoms that develop during or after an infection consistent with COVID-19 that continue for more than 12 weeks, and cannot be explained by an alternative diagnosis.[1] No correlation has been shown between disease severity at primary infection and post-acute disease.[2–4] Yet, in adults

Abbreviations: CPET, cardiopulmonary exercise testing; ECG, electrocardiogram; MIS-C, multisystem inflammatory syndrome in children.

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hospitalized at the time of acute infection, the percentage of post-COVID sequelae can be as high as 87.4%.[2–4] The acute phase of COVID-19 in children is commonly less severe than in adults.[5] However, although not extensively investigated, long-term effects of COVID, including school absenteeism, have also been shown in children.[5–7]

Recent reports from Italy and the United Kingdom suggest long-COVID also occurs in children. Nevertheless, there remains a lack of information and consensus regarding the incidence and risk factors of long-term effects of COVID in children.[8,9] Ludvigsson published a five-patient case series identifying that children display long-COVID symptoms similar to those in adults: persistent fatigue, headache, and concentration difficulties.[10,11]

Conversely, a small group of hospitalized children with COVID-19, described by Denina et al.,[7] were found not to display long-term sequelae 19–46 days after admittance.

The primary aim of this observational study was to determine how large the pediatric population is with long-COVID that has already been referred to a specialist by a family doctor.

In addition to this, we illustrate and identify specific disease characteristics through the use of a detailed case series. We conclude that long-COVID is not limited to adults, and is an overlooked phenomenon in children.

2 | MATERIALS AND METHODS

2.1 | Study design and subjects

Between December 18, 2020 and February 6, 2021, we performed a cross-sectional observational study using a survey to investigate Dutch pediatricians' experience with long-COVID in children.

In the Netherlands, when a child is sick, unless their condition is acutely life-threatening, they are seen by their family doctor. Here, the decision is made if a referral to a pediatrician is necessary since the symptoms or consequences are sufficiently serious, or the presentation not fully understood. Pediatricians work in secondary and tertiary care hospitals. The survey targeted all pediatricians. It used an online survey platform (LimeSurvey), compliant with general data protection regulation & European Union law. The survey was distributed with the help of the Dutch Pediatric Society (Nederlandse Vereniging van Kindergeneeskunde, NVK).

The survey aimed to achieve a representative distribution of at least 70% of the 73 hospitals across the Netherlands with pediatric departments. It was designed by a team of pediatricians with input from medical ethics officers and privacy advisors. All patient data were anonymized and handled in accordance with the General Data Protection Regulation. The survey, consisting of five questions with sub-questions, focused on four key areas: (1) the occurrence of Pediatric Long-COVID, (2) the clinical manifestation, (3) the severity of disease and impact on daily activity, and (4) the wider multidisciplinary team involvement. Additional information, including patient age, the investigation used to diagnose COVID and whether hospital admission was required were also collected. The respondents were given a definition of long-COVID as well as a list of predominant symptoms in adults, and were able to consult their patient records to accurately describe relevant patient cases. It was defined as cases, similar to those in adults, where symptoms such as persistent tiredness, headaches, dyspnea, concentration problems, depression, skin lesions, and gastro-intestinal complaints persisted months after initial COVID-19 infection. They were also able to fill in "other complaints."

Survey responses were excluded from the study if data regarding the number of patients, mode of diagnosis, disease course, and hospital admission were incomplete.

2.2 | Description of illustrative cases

All patients herein, during the study period, were under the care of the Pediatric Department at the Emma Children's Hospital, Amsterdam University Medical Center, Tergooi Hospital, and the Catharina Hospital. Information regarding patient characteristics, medical history, diagnostics, and clinical course were retrieved from patient files. For the patient case series patients and parents provided consent and assent. Patient data in the survey was collected by treating physicians and was completely anonymized for the study team.

3 | RESULTS

3.1 | Survey among pediatricians

Surveys from 57 hospitals were completed, covering 78% of hospitals with a pediatric department across the Netherlands. A total number of 89 children suspected of long-COVID were described with a median age of 13 years (IQR: 9–15). Of these 89, 47 (52.8%) of the reported children had a positive PCR test, 31 (34.8%) positive serology tests, and 34 (38.2%) could be diagnosed clinically. It is important to note that there is a certain overlap in these groups, a number of patients were reported to have both positive PCR and serology, and/or medical history fitting a previous COVID-19 infection. In eight (9.0%) children it was unknown how COVID-19 had been diagnosed.

The most common long-term complaint was fatigue (87%), followed by dyspnea in more than half of the children (Table 1). Many patients reported some degree of cognitive dysfunction, with 45% reporting concentrating difficulties, 13% reporting memory loss, and a further 2% describing brain fog. A further 38% suffered from headaches. Only two children presented with persistent fever, and only one had a loss of smell and taste. Table 1 gives a summary of these results. It is important to note that 18% of all children were admitted to the hospital due to their long-COVID disease presentation, of which the exact reasons are unknown to us.

TABLE 1 Results – Patient characteristics, survey

Total number of children	89	
The median age of children	13 (IQR: 9–15)	
Age range	2–18	
Positive PCR tests	47	52.8%
Positive serology tests	31	34.8%
Positive medical histories	34	38.2%
Unknown	8	9.0%
Complaints		
Fatigue	77	87%
Dyspnea	49	55%
Concentration difficulties	40	45%
Headaches	34	38%
Thoracic pain complaints	31	35%
Stomach ache	29	33%
Myalgia	25	28%
Diarrhea	21	24%
Memory loss	12	13%
Cardiac palpitations	16	18%
Skin irritation/lesions	6	7%
Dizziness	3	3%
Brain fog	2	2%
Weight loss	2	2%
Loss of appetite	2	2%
Persistent fever	2	2%
Other[a]	8	9%
Total admitted to the hospital because of long-COVID[b]	16	18%
Limitations in daily functioning		
No limitations	7	8%
Mild limitations in daily functioning[c]	43	48%
Severe limitations in daily functioning[d]	32	36%

[a]Like coughing (1%), myocarditis (1%), and anosmia (1%).
[b]For unknown reasons.
[c]For example, can go to school but excessively tired.
[d]For example, less or no school possible.

At the time of Long-COVID diagnosis, 48% reported mild limitations (e.g., can go to school but excessively tired), with 36% experiencing severe limitations demonstrated by limited or no school attendance, while only 8% of the reported patients had no disruption to their life due to their symptoms, as is shown in Table 1. 29% patients required active input from the wider multidisciplinary team: 25% required physical therapy, and 16% were seen by a psychologist.

TABLE 2 Additional referrals

Involved medical disciplines		
Required additional treatment by (para)medical disciplines	26	29%
Physiotherapy	22	25%
Psychologist	14	16%
Rehabilitation specialist	10	11%
tertiary care pediatrician	8	9%
Other		
Pediatric cardiologist	3	3%
Dietician	2	2%
Sports doctor	2	2%
Pediatric pulmonologist	1	1%
Pediatric nephrologist[a]	1	1%
Ear, nose, and throat specialist	1	1%
Occupational therapist	1	1%
School doctor	1	1%

[a]Due to kidney failure.

Three patients required a referral to a pediatric cardiologist for unspecified reasons (Table 2). One patient had kidney failure and was subsequently seen by a pediatric nephrologist. It is unclear if there is a causal link with the diagnosis of long-COVID.

3.2 | Case series

This illustrative case series consists of six children (four males), referred by general practitioners to pediatricians (Table 3). All patients fulfilled the described criteria for long-COVID in adults, with symptoms still present 12 weeks after the acute phase, a positive diagnosis of COVID-19 (either by laboratory testing or positive family history, combined with complaints fitting COVID-19).[1]

3.3 | Course of disease

Shortness of breath was the most common symptom reported by all patients during the acute COVID-19 illness. Three patients (patients 1, 2, and 5) were initially treated for a suspected asthma exacerbation with little effect seen in patients 2 and 5. Patient 1 had a history of asthma and reported an acute worsening of his pre-existing asthma symptoms, in addition to other complaints, after the acute viral infection, experienced in March 2020. He benefited from short-acting beta-agonists but still experienced many complaints. Patient 4 was treated unsuccessfully with a course of azithromycin following continued complaints and persisting fever, three months after acute COVID-19. Patients 3, 5, and 6 are still experiencing extreme fatigue,

TABLE 3 Pediatric cases with long-COVID as treated by CB, EL, and LvdS

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age/gender	11 years/M	13 years/F	13 years/M	4 years/M	17 years/M	17 years/F
Medical history	• Asthma • (2010) Pneumonia • Eczema	• Asthma • (2017) Pneumonia	• History of eczema • (2007) RSV bronchiolitis	• Cow's milk allergy	• Asthma • Allergic rhinitis • Scoliosis • Autistic spectrum disorder	Breast reduction
Acute COVID	March 2020	March 2020	August 2020	March 2020	March 2020	September 2020
Long-COVID consult date	December	December	October	August	September	November
Symptoms of acute COVID-19	• Fever • Shortness of breath • Thoracic pain	• Fever • Shortness of breath • Thoracic pain • headache	• Coughing • Anosmia (3 weeks)	• Fever • Runny nose • Shortness of breath • Fatigue • Dizziness • Stomach ache • Change in bowel habits • Skin rashes • Generalized myalgia	• Fever • Dyspnea	• Cardiac palpitations • Generalized myalgia • Balance problems • Changes in bowel habits • Fatigue • Shortness of breath
Hospitalization	No	No	No	No	No	No
Initial treatment	Salbutamol (with effect), fluticasone propionate	Salbutamol (no effect)	None	Broad-spectrum antibiotics	Fluticasone/salmeterol & Physiotherapy	None
Infection source	Parents (medical history)	Parents (medical history)	Parents (RT-PCR positive)	Parents (RT-PCR positive)	Unknown	Unknown
Symptoms of long-covid	• Fatigue • Thoracic pain • Shortness of breath • Coughing • Dizziness • Thoracic palpitations • (Severe) headaches	• Fatigue • Shortness of breath • Thoracic pain • Dizziness • Nausea • Light-headed • Headaches	• Fatigue • Cognitive dysfunction • Weight loss • Headaches • Exercise intolerance	• Fever (intermittent) • Fatigue • Change in bowel habits • Abdominal pain • Difficulties breathing • Skin rashes • Generalized pain	• Shortness of breath • Fatigue • Thoracic pain • Coughing	• Thoracic pain • Fatigue • Cardiac palpitations • Abdominal pain and abnormal stool • Headaches • Dizziness
Missing school	Yes	Yes	Yes	n/a	Yes	Yes

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
COVID test	**PCR**	Not done	Not done	Not done	Not done	Negative	Positive
	Serology results	Negative	Negative	Positive	Negative	Positive	Not done

TABLE 3 (Continued)

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Blood tests	**Full blood count**	Not done	Normal	Normal	Normal	Normal	Normal
	Inflammation markers	Not done	• ESR 20 mm/h • CRP 10 mg/L	Normal	Normal	Normal	Normal
	kidney function	Not done	Normal	Normal	Normal	Normal	Normal
	liver function	Not done	Normal ALP 345 U/L (high)	Normal	Not done	Not done	Normal
	thyroid function	Not done	Not done	Normal	Normal	Not done	Not done
	Other	Not done	• *H. pylori* in feces negative	• Feces TFT negative • Serology for EBV negative • IgG CMV positive • Normal lymphocyte subsets	• Celiac disease excluded • normal 25OH-VitD 2 + 3 • PCR for SSYC and parasites negative in feces	• Fecal calprotectin level: normal.	• Normal electrolytes • Normal blood gas • Normal PT-INR • Normal D-dimer • Negative pregnancy test
Cardiac evaluation	**ECG/Holter**	Right axis deviation (135°)	Normal	Normal (stress ECG: normal)	• Incomplete right bundle branch block (no earlier ECG available) • Holter: normal sinus rhythm. Sinus tachycardia at time of complaints	Normal	Negative T wave in V3 and III (ECG before COVID-19 showed a negative T wave in II, but not in V3)
	Echocardiogram	Normal	Not done	Normal	Normal	Not done	Not done
Pulmonary evaluation	**CT-thorax**	Not done	Not done	Normal	Not done	Normal	Normal
	Chest X-ray	Not done	Not done	Not done	Normal	Not done	Not done
	Flow-Volume	FVC 84% and 97%, FEV1 81% and 99% before and after administration of salbutamol	FVC 102% and FEV1 102.4% after salbutamol	FVC 81% and FEV1 81% after salbutamol	Not done	FVC 90% and FEV1 93% after salbutamol	FVC 80% and FEV1 87% after salbutamol
	Pattern	Obstructive curve	Normal	Normal		Normal	Normal
	Reversibility	Fully reversible	No	No		No	No

(Continues)

TABLE 3 (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Body plethysmography	Not done	Not done	TLC 76%, RV 74%	Not done	Normal	TLC 88%; RV 86%
CO diffusion capacity	Not done	Not done	Normal	Not done	Normal	Normal (111%)
Exercise testing	Not done	Treadmill test: • maximum heart frequency 173/min • O_2 saturation: 97%–99%. • Dyspnea in line with dysfunctional breathing	CPET: VO_2 max: 24 ml/min kg (51%), HF max: 163/min. RER 1.18: conclusion: dysfunctional breathing and reduced physical fitness, no circulatory nor ventilator abnormalities.	Not done	Treadmill test: Anxiety during testing with hyperventilation due to exhaustion. No signs of exercised induced bronchoconstriction, SaO_2 reduced to 90% while exercising.	Not done

Abbreviations: ALP, alkaline phosphatase; CMV, cytomegalovirus; CPET, cardiopulmonary exercise testing; EBV, Ebstein Barr Virus; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 s; FT4, free thyroxin fraction; FVC, forced vital capacity; HF, heart frequency; INR, International Normalized Ratio; N/a, not applicable; O_2, oxygen; RER, respiratory exchange rate; RV, residual volume; SSYC, Shigella, Salmonella, Yersinia, Campylobacter; TFT, triple feces test; TLC, total lung capacity; TSH, thyroid stimulation hormone; VO_2 max, maximum oxygen absorption.

resulting in school absence. Patients 3 and 6 are treated by a specialist in pediatric rehabilitation, while patients 2 and 5 are treated by a physical therapist. Patient 6 was living independently before COVID-19 diagnosis, but had to move back in with her parents due to her long-lasting symptoms.

4 | DISCUSSION

Our study shows that long-COVID is also present in children and that the main symptoms resemble those previously described in adults.[2–4] It is one of the first studies to provide nationwide data on the extent of long-COVID as a new disease entity in children and highlights that long-COVID can seriously affect children of all ages. Long-COVID leads to limitations in daily functioning in the majority of children reported here.

In a single-center study from Italy by Buonsenso et al.,[8] persistent symptoms in children previously diagnosed with COVID-19 were also reported in 42.6% of children that had been presented with COVID-19 to that hospital. The reported long-COVID symptoms in this Italian study showed resemblance to the symptoms reported in our study, although the prevalence differed. A possible explanation could be that the children described in our study were all identified by Dutch pediatricians. Consequently, these children had severe enough complaints to get referred to the pediatrician by the general practitioner, which may also explain the higher percentage of children with limitations in daily functioning in our study compared to the Italian group.

Ludvigsson et al., reported in November 2020 a five-patient case series on long-COVID in children, where none of the children were able to attend school 6–8 months after the acute-COVID.[10] These cases resemble the findings in our study.

The varying presentation of pediatric long-COVID, will, without a standardized diagnostic plan, result in a varying diagnostic approach, as shown by our patient case series.

Our study has several strengths. First, the survey response rate was high, including 78% of all hospitals, providing a national, pediatric, representative sample. Second, we were able to assess the most common symptoms directly from the treating physicians. Third, our cases highlight the challenges faced by health care professionals taking care of these children. This study clearly identifies the need for an international consensus and guideline on long-COVID in children.

Our study also has some limitations. We only collected data from pediatricians working in general and university hospitals, and not from family doctors. We expect that the more severe cases of long-COVID will be referred to the pediatrician and that milder cases may be underrepresented in our study. The type of symptom may also prompt referral, which could be a reason for the high percentage of patients suffering from fatigue and breathlessness. Second, due to privacy considerations, limited clinical data was collected in the questionnaire.

Therefore, data on comorbidities, pre-existing disease, height, weight, psychological status, and diagnostic workup are missing. Third, only retrospective data were obtained from pediatricians. While they were able to consult their records, this may still have led

to a recall bias, and thus an underestimation of total cases, and potentially an overrepresentation of severe cases.

What are the clinical implications of our study? In the Netherlands 139,221 children have tested positive for SARS-CoV-2, since the beginning of the outbreak in the Netherlands on February 27, 2020 (as published February 9, 2021).[12] In relation to the total number of children tested positive for SARS-CoV-2 in the Netherlands, the number of 89 patients reported in our survey seems small. However, we suspect that these children represent the tip of the iceberg since some children with long-COVID may only be treated by the general practitioner. Furthermore, long-COVID is still an unknown phenomenon to many pediatricians, likely resulting in underdiagnosing. Nevertheless, we can conclude that long-COVID is a disease entity in children. This study does not yet inform us about the incidence and risk factors of long-COVID in children, but it seems to be relatively rare. Severe acute COVID-19 in children leading to hospital presentation and/or admission is also infrequent, as demonstrated in our national cohort study, the COPP study.[13] Children in general experience additional impact on mental and social health due to governmental restrictions, and this might also influence occurrence and course of long-COVID in children.[14]

Long-term sequelae of COVID-19 in children have been less well described than in adults and data on possible long-term sequelae of COVID-19 in children needs to be collected and shared on a national and international level. Not only severe acute COVID cases but also mild acute COVID cases with long-COVID need our attention. Long-COVID in children exists and leads to high morbidity and limitations in daily functioning. Increased awareness is needed to perform prospective follow-up studies and multidisciplinary, evidence-based guidelines for diagnosis and treatment.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Caroline L. H. Brackel: Conceptualization (lead); data curation (equal); formal analysis (equal); methodology (equal); project administration (equal); supervision (equal); writing – original draft (lead); writing – review & editing (lead). **Coen R. Lap**: Conceptualization (equal); data curation (lead); formal analysis (lead); investigation (equal); methodology (equal); project administration (equal); software (equal); writing – original draft (equal). **Emilie P. Buddingh**: Conceptualization (supporting); writing – review & editing (equal). **Marlies A. van Houten**: Conceptualization (lead); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review & editing (equal). **Linda J. T. M. van der Sande**: Conceptualization (equal); formal analysis (equal); writing – original draft (equal); writing – review & editing (equal). **Eveline J. Langereis**: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); supervision (supporting); writing – original draft (equal); writing – review & editing (equal). **Michiel A. G. E. Bannier**: Conceptualization (equal); writing – review & editing (supporting). **Marielle W. H. Pijnenburg**: Conceptualization (supporting); writing – review & editing (supporting). **Simone Hashimoto**: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); project administration (equal); software (equal); supervision (lead); writing – original draft (equal); writing – review & editing (equal). **Suzanne W. J. Terheggen-Lagro**: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); supervision (lead); writing – original draft (equal); writing – review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

SUMMARY

Long-COVID in children is a new phenomenon that calls for a multidisciplinary approach and (inter)national collaboration.

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