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

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 disease2–4. Yet, in adults...
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.5,7 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 al-
ready 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 con-
clude 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 pre-
sentation 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 dis-
tributed 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 multi-
disciplinary team involvement. Additional information, including pa-
tient age, the investigation used to diagnose COVID and whether
hospital admission was required were also collected. The re-
pondents 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 regard-
ning 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 pro-
vided 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 hospi-
tals 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 infec-
tion. 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 rea-
sons are unknown to us.
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. 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 | Asthma (2017) Pneumonia | History of eczema (2007) RSV bronchiolitis | Cow’s milk allergy | Asthma | Allergic rhinitis | Scoliosis | Autistic spectrum disorder |
| **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            | Fever            | Coughing         | Fever            | Fever            | Fever            |                   |
| Shortness of breath | Shortness of breath | Anosmia (3 weeks) | Shortness of breath | Runny nose       | Dyspnea          |                   |
| Thoracic pain    | Thoracic pain    |                   |                   | Shortness of breath |                   |                   |
|                   |                   |                   |                   | Dizziness        |                   |                   |
|                   |                   |                   |                   | Stomach ache     |                   |                   |
|                   |                   |                   |                   | Change in bowel habits |                   |                   |
|                   |                   |                   |                   | Skin rashes      |                   |                   |
|                   |                   |                   |                   | Generalized myalgia |                   |                   |
| **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           | Fatigue           | Fatigue           | Fatigue           | Fatigue           | Shortness of breath |                   |
| Thoracic pain     | Shortness of breath | Cognitive dysfunction | Fatigue           | Fatigue           | Fatigue           |                   |
| Shortness of breath | Thoracic pain    | Weight loss       | Change in bowel habits |                   |                   |                   |
| Coughing          | Dizziness         | Headsches         | Abdominal pain    |                   |                   |                   |
| Dizziness         | Nausea            |                   | Difficulties breathing |                   |                   |                   |
| Thoracic palpitations | Light-headed    | Exercise intolerance | Skin rashes      |                   |                   |                   |
| (Severe) headaches | Headaches         |                   | Generalized pain  |                   |                   |                   |
| **Missing school** | Yes              | Yes              | Yes              | n/a              | Yes              | Yes              |
| **COVID test**    | PCR              | PCR              | PCR              | PCR              | PCR              | PCR              |
| **Serology results** | Not done         | Not done         | Not done         | Not done         | Negative         | Positive          |
|                  | Negative          | Positive         | Negative         | Positive         |                  | Not done          |
|                         | 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**|                 |                 |                 |                 |                 |                 |
| ESR                     | Not done        | Normal 20 mm/h  | Normal          | Normal          | Normal          | Normal          |
| CRP                     | Not done        | CRP 10 mg/L     | Normal          | Normal          | Normal          | Normal          |
| **kidney function**     |                 |                 |                 |                 |                 |                 |
| ALP, 345 U/L (high)     | Normal          | Normal          | Normal          | Normal          | Normal          | Normal          |
| **liver function**      |                 |                 |                 |                 |                 |                 |
| ALP                     | Not done        | Normal ALP 345 U/L (high) | Normal          | Not done        | Not done        | Not done        |
| **thyroid function**    |                 |                 |                 |                 |                 |                 |
|                         | Not done        | Not done        | Not done        | Normal          | Normal          | Not done        |
| **Other**               |                 |                 |                 |                 |                 |                 |
| H. pylori in feces      | negative        |                 |                 |                 |                 |                 |
| Feces TFT negative      | Normal          |                 |                 |                 |                 |                 |
| Serology for EBV        |                 |                 |                 |                 |                 |                 |
| negative                |                 |                 |                 |                 |                 |                 |
| IgG CMV positive        | Normal          |                 |                 |                 |                 |                 |
| Normal lymphocyte subsets |                 |                 |                 |                 |                 |                 |
| Celiac disease          | Not done        |                 |                 |                 |                 |                 |
| excluded                |                 |                 |                 |                 |                 |                 |
| 25OH-VitD 2 + 3         | Normal 20 mm/h  |                 |                 |                 |                 |                 |
| PCR for SSYC and parasites negative in feces | Normal          |                 |                 |                 |                 |                 |
| Fecal calprotectin level: normal. | Normal          |                 |                 |                 |                 |                 |
| Normal electrolytes     | Normal          |                 |                 |                 |                 |                 |
| Normal blood gas        | Normal          |                 |                 |                 |                 |                 |
| Normal PT-INR           | Normal          |                 |                 |                 |                 |                 |
| Normal o-dimer          | Normal          |                 |                 |                 |                 |                 |
| Negative pregnancy test | Normal          |                 |                 |                 |                 |                 |
|                         |                 |                 |                 |                 |                 |                 |
| **Cardiac evaluation**  |                 |                 |                 |                 |                 |                 |
| ECG/Holter Right axis deviation (135°) | Normal          | Normal (stress ECG: normal) | Normal          | Normal          | Normal          | Normal          |
|                         |                 |                 |                 |                 |                 |                 |
|                         |                 |                 |                 |                 |                 |                 |
| **Echocardiogram**      |                 |                 |                 |                 |                 |                 |
| Normal                  |                   |                 |                 |                 |                 |                 |
|                         |                 |                 |                 |                 |                 |                 |
| **Pulmonary evaluation**|                 |                 |                 |                 |                 |                 |
| CT-thorax               | Not done        | Not done        | Normal          | Normal          | Normal          | Normal          |
| Chest X-ray             | Not done        | Not done        | Not done        | Not done        | 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          | Normal          |
| Reversibility           | Fully reversible | No              | No              | No              | No              | No              |

(Continues)
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. 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., 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. 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). 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. 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.

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. Budding: 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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