COVER PAGE

Title: International Care programs for Pediatric Post-COVID Condition (Long COVID) and the way forward.

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Category of study: Clinical study

Impact:

- Pediatric Post-COVID Condition (PPCC) Care programs have been initiated in many countries.
- Children with PPCC in different countries are affected by similar symptoms, limiting many to participate in daily life.
- There is substantial heterogeneity in diagnostic testing. Access to specific diagnostic tests is required to identify some long term COVID-19 sequelae. Treatments provided were limited to physical therapy and psychological support.
- This study emphasizes the need for evidence-based diagnostics and treatment of PPCC. The International Post-COVID Collaboration for Children (IP4C) provides guidance for guideline development and introduces a framework of priorities for PPCC care and research, to improve PPCC outcomes.

ABSTRACT

Background:

Pediatric Post-COVID-Condition (PPCC) clinics treat children despite limited scientific substantiation. By exploring real-life management of children diagnosed with PPCC, the International Post-COVID-Condition in Children Collaboration (IP4C) aimed to provide guidance for future PPCC care.

Methods:

We performed a cross-sectional international, multicenter study on used PPCC definitions; the organization of PPCC care programs and patients characteristics. We compared aggregated data from PPCC cohorts and identified priorities to improve PPCC care.

Results:

Ten PPCC care programs and six COVID-19 follow-up research cohorts participated. Aggregated data from 584 PPCC patients was analyzed. The most common symptoms included fatigue (71%), headache (55%), concentration difficulties (53%) and brain fog (48%). Severe limitations in daily life were reported in 31% of patients. Most PPCC care programs organized in-person visits with multidisciplinary teams. Diagnostic testing for respiratory and cardiac morbidity was most frequently performed and seldom abnormal. Treatment was often limited to physical therapy and psychological support.

Conclusion:

We found substantial heterogeneity in both the diagnostics and management of PPCC, possibly explained by scarce scientific evidence and lack of standardized care. We present a list of components which future guidelines should address, and outline priorities concerning PPCC care pathways, research and international collaboration.

TEXT

Introduction

Long-term SARS-CoV-2 sequelae as established in adults have also been recognized in children.[1-3] Prevalence rates of Pediatric Post-COVID Condition (PPCC) vary markedly between studies, ranging from 1.6 to 70%.[4-6] Children with PPCC suffer from a wide range of symptoms, with variable impact on daily life. They often seek support from health care professionals, and in response to this demand, specialized PPCC clinics have been set up in many countries.[3,6] No standard approach on how to provide adequate care has been established, due to a scarcity on evidence-based guidance. Consequently, care provided around the world may not sufficiently meet the needs of children with PPCC.[7-9]

We therefore endeavored to share and explore real-life management of children with PPCC in different settings globally, by bringing clinicians, researchers and children affected by PPCC and their representatives together in a collaborative network, the International Post-COVID Collaboration (IP4C), to share experiences and subsequently determine the requirements for global guidelines and future development of PPCC care and research.

Methods

Participants and study design

Between June and September 2021, physicians and researchers from 16 universities who had joined IP4C and were either involved in developing and managing PPCC care programs or in standardized follow-up programs for children with acute COVID-19, were invited to join this study. Together, we performed a retrospective, cross-sectional analysis of fully anonymized aggregated data of PPCC patients included in care programs. Only cohorts with at least five patients were included. Ethical approval was obtained in each individual center. Data were collected using a standardized data collection form. Definitions used for PPCC by each of all 16 universities were collected. A descriptive program-level and patient-level analysis was performed in respectively 10 and 9 PPCC care programs. (Efigure 1, Etable 1).

PPCC care and research outcomes

Since December 2021, IP4C has organized regular meetings to discuss and share experiences of recent scientific developments, data harmonization tools, complex PPCC cases, and current priorities in PPCC research and care. Based on these expert discussions and the study data, we formulated a list of minimal requirements which future PPCC guidelines should address and a framework of global priorities for PPCC research and diagnostic and care pathways to inform clinical management guidelines. These were informed by all study contributors, and representatives from LongCOVID Kids, a global patient support organization.

Results

Care Program-Level Analysis:

The definitions used for PPCC by all 16 universities varied widely in their duration of symptoms required, symptom progression, and the classifications for a history of acute COVID-19. (Efigure 1, Etable 2 and 3). In eight out of ten included PPCC care cohorts, children were treated by multidisciplinary teams in outpatient settings, involving a broad variety of medical specialists. Seven care cohorts offered online follow-up visits and in seven cohorts 4-18% of their patients were admitted for diagnostic testing or due to the severity of their PPCC symptoms. (Efigure1, Figure 1C and 1G). Duration of follow-up ranged from 3 to 13 months, or until full recovery, with some patients still under care at the time of data collection.

Patient-Level Analysis

Nine out of ten care cohorts already had started to include patients in their care programs and shared data from 584 children in total. (eFigure 1, Figure 1A and B).

Characteristics of PPCC patients: The representation of females was higher in seven out of nine cohorts, with a median (range) of 62% (40-70%). Preceding PPCC, nearly all experienced an asymptomatic or mildly symptomatic (88-100%) COVID-19 infection. The range of impact of PPCC varied, with 17% (0-70%) of children with PPCC suffering no limitations in daily life; 24%

(6-70%) suffered mild limitations (chronic complaints and > 75% school attendance); 24% (6-70%) suffered severe limitations (with <75% school attendance) and 1.6% (0-9%) suffered very severe limitations in daily life (bedridden for > 50% of the time). The symptoms experienced were similar among cohorts, although prevalence differed. (Figure 1D, Etable 4)

Diagnostic test results: Diagnostic tests for respiratory and cardiac morbidities were performed in most care cohorts but were seldom abnormal. The exception was spirometry with reversibility testing, which was performed in a median of 27% (range 8-91%) of patients. This test revealed abnormalities in some of the cohorts (26% (range 0-100%)). Abnormalities were also detected by less commonly performed tests. For example, the cardiac MRI, performed in a median of 4% (1-18%) of patients revealed abnormalities in 17% (0-67%). Another example is thoracic CT imaging with contrast, which was performed in only 12 patients across all cohorts and showed abnormalities in two of those patients. All cohorts performed different types of assessments for physical functioning and aerobic capacity and the frequency of abnormal test results again varied widely. Postural orthostatic tachycardia syndrome (POTS) analysis was performed in five cohorts in 30% (5-80%) of children, and 30% (0-63%) of those tests revealed abnormalities. Different self-administered questionnaires were administered to patients, focusing on areas such as fatigue, neurocognitive functioning, depression/anxiety, and attention/concentration difficulties. The percentage of children with abnormal results were as follows: fatigue 14% (0-27%); neurocognitive functioning 77% (0-100%); depression/anxiety 26% (23-65%); and attention/concentration difficulties 37% (12-62%) (Figure 1E). Details concerning the type of test performed are described in eTable5.

Type of treatment: The treatments varied across the cohorts typically involving either physical therapy, pediatric occupational therapy, and/or psychological support. In most cohorts, it was observed that interventions frequently focused on lifestyle modifications. These modifications targeted various aspects including sleep patterns, physical activity, diet, and school. Interventions concerning mental health were also prevalent across the cohorts. Complementary medicine was exclusive to two cohorts, both of which were based in the United States (Figure 1F).

Priorities for PPCC care and research

Based on our study results, a minimal required set of topics which future guidelines should address was agreed upon via consensus focusing on identification and evaluation of patients, identifying treatable traits and important items to address while treating PPCC patients. (Figure 2). In addition, a framework of key priorities for PPCC research and organization of care was formulated to guide researchers, clinicians, funders, public health and health management policy makers, to inform actions to improve long term PPCC outcomes for all. (Figure 3).

Discussion

This study provides the first real-world multicenter snapshot of the diagnosis and treatment approaches used in different countries for children suspected of having PPCC. Our study shows that children in different countries are affected by similar PPCC symptoms, in many impacting on their ability to carry out daily activities and attend education which may have wider social implications. This is a concern especially at their formative years, and the long-term impact is unknown.

In general, PPCC is approached as a multisystem disease, and diagnosed and treated by multidisciplinary teams. Standard screening tests such as electrocardiogram and spirometry do not sufficiently shed light on PPCC's pathophysiology, yet they are critical for evaluating its differential diagnosis. The frequency of more in-depth evaluation varied substantially, which was surprising considering existing adult guidelines recommending a wide range of assessments.[7] Pediatric case reports have also suggested that thorough evaluation may lead to more targeted management.[11]

This analysis underscores that PPCC care programs lack consensus concerning diagnostics and therapeutics, highlighting a need for further research into etiology, and treatments to inform evidence based guidelines and organization of care. We hypothesize that these differences stem from differences in local policies, the different medical specialist involved at each center and a lack of experience with and understanding of PPCC by the medical community as a whole during the time of data collection. Similarities between programs are mostly due to healthcare providers making the same pragmatic choices based on their expert opinion, their knowledge of other post-viral illnesses and evidence emerging on adult Post Covid Condition (PCC).

The way forward

Our data show a need for standardized, comprehensive evidence-based guidance on diagnostic and therapeutic approaches; and a more nuanced differentiation between patients, to determine which children require what type of diagnostic evaluations, based on symptoms and burden of disease. A symptom driven evaluation focusing on exclusion of differential diagnoses should be part of the diagnostic pathway. To facilitate this, international guidelines are much needed. During the period this study was performed, IP4C team-members and others have contributed to the development of a post-COVID Core Outcome Set (PC-COS) for children and young people.[12] This PC-COS aimed to be included in a standardized work-up in all children suffering from PPCC (source). In addition, multiple articles have recently been published, in which local or national clinical care programs are described.[13-17] The World Health Organization has developed PCC guidelines mainly aimed at adults, which also provides information for PPCC and patients affected[16]. They recently published a self-management leaflet focusing on adolescents with PPCC[17]. The American Academy of Physical Medicine and Rehabilitation published a multi-disciplinary consensus statement for PPCC diagnostics and treatment based on a modified Delphi procedure.[13] These examples provide guidance on both diagnostic work-up and treatment modalities in children with PPCC, but do not address all items listed in figure 2, further adding to heterogeneity in care. IP4C which is an open collaboration, aims to bring these examples together to inform and advocate for harmonized evidence based guidelines and trials to inform diagnostic, care and outcomes for children with PPCC globally, while recognizing that further work is needed to explore access to care for children with PPCC in lower resource settings.

Most of the therapeutic interventions prescribed in our cohorts are derived from other post-viral syndromes but lack scientific substantiation and evidence for effectiveness in PPCC. Most were focused primarily on rehabilitation care. Despite the number of children and young people affected by PPCC worldwide, research concerning PPCC is still scarce. IP4C acknowledges lack of evidence as a main reason for lack of uniformity between care programs and the difficulty of developing a PPCC guideline. In adults, Long COVID Europe and WHO Europe have acknowledged this and are advocating governments and health authorities to focus on PCC, by improving recognition and knowledge sharing by fully equipped health systems; well-coordinated research; and evidence-based, safe and effective rehabilitation.[18-19] PPCC deserves the same priority.

With our framework, we aim to provide guidance in setting our priorities concerning PPCC research and organization of care. To realize these priorities, we advocate for investments in health care systems, research programs, international collaboration and guideline development dedicated to PPCC, in order to improve short- and long-term outcomes of children living with PPCC worldwide.

Data availability statement: The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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FIGURE LEGENDS

Figure 1:

Organization of care, diagnostics and interventions in 10 PPCC care cohorts. 1a: Participating countries in study. From most countries 1 university is represented in this study, with the exception of United States of America (3). 1b: Number of patients for each cohort. 1c: Location of care. §The cohort from Jena University Hospital included patients from both an academic and general hospital. 1d: Symptoms of PPCC patients in PPCC care cohorts. Data shown as median and range of median values (percentages of patients). & e.g., tics, seizures, nonepileptic spells. * no general definition was used. 1e: Percentage of total patients in PPCC cohorts in whom test is performed and in whom test was abnormal (% of test performed). Data available for 9 cohorts. Data shown as median and range of median values of all cohorts, only shown for cohorts where these specific tests are performed. #) Spirometry + albuterol: spirometry with reversibility testing; spirometry-: spirometry without reversibility testing. %) Measured during inclusion in cohort. *) questionnaires concerning daily functioning, health domains and quality of life. ^) other, namely research tests, lung SPECT CT. CO: Carbon Monoxide; CPET: cardiac pulmonary exercise test (incl VO2 max measurement); EEG: electroencephalography; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; NCF: neurocognitive functioning; POTS: Postural orthostatic tachycardia syndrome; Q: questionnaire, QoL: Quality of Life. 1f: Therapy prescribed in PPCC cohorts, size of box represents number of cohorts using this type of therapy. Data available for 8 cohorts. CBT: cognitive behavioral therapy; @) ASP: activity schedule pacing. 1g: Type of health care providers involved in care programs.

Figure 2:

Minimal required set of topics future international PPCC guideline should address.

Figure 3:

IP4C framework: Priorities in PPCC care, research and international collaboration

Statements and Declarations:

Funding:

Prof. Stephenson, Dr. Pinto Pereira and Dr. Shafran Dr. Manjula Nugawela were funded by the Department of Health and Social Care, in their capacity as the National Institute for Health Research (NIHR), and by UK Research & Innovation (UKRI), who have awarded funding grant number COVLT0022. The department of Health and Social Care, as the NIHR, and URI were not involved in study design, data collection, analysis or interpretation of the data, nor the writing of the present study or the decision to submit the article for publication. All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, UKRI or the Department of Health. All other authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interest:

Dr. Sigfrid received support by the UK Foreign, Commonwealth and Development Office and Wellcome [215091/Z/18/Z] and the Bill & Melinda Gates Foundation [OPP1209135]. Dr. Oliveira and Dr. Paintsil were supported, in part, from grants by the National Institutes of Health (NIH) to Dr. Oliveira (K23AI159518), its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIH. All other authors have no conflicts of interest relevant to this article to disclose.

Contributors Statement:

Dr. Brackel, Dr. Noij conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript and reviewed and revised the manuscript. Ms. Legghe, Dr. Vijverberg, Prof. Maitland-van der Zee, Prof. Goudoever, Dr. Hashimoto and Dr. Terheggen-Lagro conceptualized and designed the study, critically reviewed the analyses, and reviewed and revised the manuscript.

Dr. Buonsenso, Prof. Munblit, Dr. Sigfrid, Dr. Anmyr, Dr. Ashkenazi-Hoffnung, Dr. Edwards, Dr. Herrting, Dr. Lorenz, Dr. Malone, Dr. McVoy, Dr. Miller, Dr. Morrow, Dr. C. Oliveira, Dr. Paintsil, Dr. Ryd-Rinder, Dr. Shafran, Prof. Stephenson, Dr. Tosif, Dr. Villard, Dr. Vilser conceptualized the study, reviewed the data collection tools, collected data and reviewed the manuscript. Dr. Bellinat, Dr. Dias, Ms. Fashina, Dr. GjergjaJuraški, Dr. Gonçalves, Dr. Hansted, Dr. Herczeg, Dr. Jankauskaite, Dr. Kaswandani, Dr. Kevalas, Dr. Krivácsy, Mrs McFarland, Dr. Nugawela, Dr. P. Oliveira, Dr. Osmanov, Dr. Overmars, Dr. Pinto Pereira, Dr. Prawira, Dr. Dwi Putri, Dr. Ramos, Dr. Rasche, Dr. De Rose, Dr. Samitova, Dr. Savić Jovanović, Ms Say, Dr. Scott, Dr. Shachar-Lavie, Dr. Shmueli, Dr. Snipaitiene, Dr. Ténai, Dr. Turkalj, Mr. Valentini, Dr. Vasconcelos collected data and critically reviewed the manuscript.

All authors contributed to the phramework, approved the final manuscript as submitted and agree to be accountable for all aspects of the manuscript.

Ethical approval and consent to participate:

This study was performed in line with the principles of the Declaration of Helsinki. Patient consent was not required, due to the use of aggregated and fully anonymized data. Approvement was granted by the medical research ethics committee of the Amsterdam University Medical Centers, location AMC, which evaluated this project as exempt from the Medical Research Involving Human Subjects Act (WMO) (W21_550#21.606). The study was approved by each center’s institutional review board.