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Exploring Long Covid: An Unexpected Research Journey in Family Medicine Leading to Translational Research

Letter to the editor

Abstract

In the realm of day-to-day family medicine and general healthcare, where each patient's journey commences and concludes, certain enigmatic occurrences exist. These phenomena, while not yet medically explained, inflict considerable suffering and distress. A family physician chronicles the journey initiated by curiosity, one that weaves together diverse fields of study and evolves into translational research.

The pivotal inquiry revolves around comprehending the experiences of individuals whose lives have undergone profound and abrupt alterations, characterized by cognitive challenges and enduring fatigue and pain persisting for months or even years following a Covid infection. To address this question, a research project gradually took shape, with each step contributing to its development. The course of this research, unexpected and groundbreaking, is illuminated in this presentation.

keywords ;

Family Practice; Medically Unexplained Symptoms ;observational cohort study; mixed study; Post-Acute COVID-19 Syndrome; SPECT-CT; Multiomics; Translational Research, Biomedical

Long Covid as new set of medically unexplained symptoms

The practice of general medicine often serves as a focal point for research inquiries. Essentially, each patient consultation inherently poses a research question to the physician. Typically, the physician draws upon their existing knowledge or seeks guidance from established techniques and colleagues to shed light on the issue at stake. However, when faced with a novel problem lacking established techniques or specialists, the physician can feel as lost as the patient and may tend to deny the issue or conceal their lack of knowledge. Establishing a partnership with the patient offers an alternative approach to tackling the problem, all while meticulously observing the unfolding situation and leveraging international literature to advance our understanding. Long Covid epitomizes such an entirely new challenge in the practice of medicine. The steps in a family physician's research journey are explained here.

In the context of long Covid, it is apparent that patients experience an unexpected combination of medically unexplained symptoms that significantly alter their life trajectory following a SARSCoV-2 infection. Medically unexpected symptoms are the bread and butter of general practice [1] but from the very beginning, I didn't have any intentions of engaging in research. There were no project developments, no literature reviews, and no preliminary investigations. My primary focus has always been on providing family medicine consultations to my patients. I've dedicated nearly 50 years to practicing in the same town, serving the same families in Charleroi, Belgium.

Surge of the problem in a busy practice

Then, one day, a crucial question emerged. I found myself wondering why a patient who had been severely affected by Covid, one year after the acute phase of the illness, showed such remarkable and rapid improvement. This question arose in July 2021, marking the beginning of my research journey. It led me to dive into extensive reading and writing. The culmination of these efforts resulted in a manuscript, which, although initially approved for publication, faced rejection six months later when I revealed to the publisher that the patient had experienced a relapse. To my surprise, the publisher asked me not to publish. Publishers can be quite peculiar.[2]

This rejection opened up another research question: why do patients experience relapses from an illness that remains largely unknown? The journey into Long Covid brought forth many questions, especially regarding the functionality of our healthcare system and how it leaves these patients feeling abandoned. As I continued my work, an unexpected amalgamation of unexplained symptoms began to form a syndrome in my clinical observations, gradually becoming known as Long Covid.

Opening of a research path

I embarked on the creation of an online database using Google Sheets to gather quantitative data and corresponding terms for qualitative analysis with the help of students in medicine. In the meantime I started compiling a classified bibliography [2]. I was on a quest for understanding. My reading led me to Guedj et al.'s work on labeled 18 FDG PET scans [3], which prompted me to request a technetium scintigraphy (SPECT-CT), the sole isotopic examination reimbursed by my country's social security system that allowed me to examine the brain. Astonishingly, nearly all patients with severe cognitive impairment displayed alterations in cerebral vascular flow, confirming my clinical suspicion of severe neuronal damage. After studying 34 patients, I published a report on the Orbi website of the University of Liège. The magic of the Internet and social networks played their part. Patients reached out to me from afar, seeking my expertise even though they felt isolated and abandoned. The King Baudouin Foundation granted me non-renewable financial support.

Transformation of my practice

From then on, I found myself working with two distinct groups of patients with vastly different profiles and clinical stages. The first group consisted of patients whom I or my young partner had known for a very long time, hailing from our town and reflecting the typical demographic of our patient base. We are budget-conscious doctors, operating in what used to be a working-class milieu, serving coal miners, foundry workers, and later, three generations of the unemployed. Our doors were open to those without documentation, those with nothing,

and many others. Among our patients, there were few university graduates and very few tech-savvy individuals.

The second group comprised patients treated by other doctors who were desperate due to their condition but possessed considerable intellectual and technological capabilities. Many were highly educated and had no significant financial concerns before falling ill. Some had an astonishing depth of knowledge about health. A significant number belonged to Long Covid patient associations and strived to maintain social connections despite their cognitive challenges. These individuals were already seriously ill and had undergone extensive medicalization when they approached me for support. The publication of my initial research report garnered attention from other researchers, leading to an invitation to publish in the journal *Viruses*. [4]

The Covid Human Genetic Effort networks opens new horizons in biological research

Simultaneously, my literature search and network of colleagues brought forth remarkable collaborations. The COVID Human Genetic Effort, an international consortium focused on uncovering the human genetic and immunological basis of various clinical forms of SARS-CoV-2 infection, became accessible through a simple email to Professor Casanova (Rockefeller Institute).

Subsequently, my clinical observations were used at the Rega Institute in Leuven, Belgium, for transcriptomic research on blood samples generously donated by my patients, under an ethical agreement approved by the University of Leuven (KUL - Dr I. Meyts). These samples were then sent to Stockholm, Sweden, to the Brodin lab at Karolinska for proteomic studies. Genomic studies were also planned to take place at Necker in Paris. Furthermore, at the experimental neurobiology laboratory of the University of Namur, Belgium, Professor Nicaise and his doctoral student proposed studying brain organoids and behavioral disorders in mice using serum from Long Covid patients. Several patients from my cohort readily agreed to participate.

Last but not least ; steps in digital health

Lastly, in the realm of ontologies, an Australian researcher at Macquarie University, embarked on a Long Covid study, mining millions of medical records from his state (Sydney). I was put in touch with him through my participation in the Wonca International Classification Committee. Together, we aim to explore how my database, containing the words of patients, can augment a Long Covid ontology. The team at my medical informatic laboratory in Rouen, France, thanks to its multi-terminology health portal (HeTOP - Prof Darmoni & Grosjean) is enthusiastic about taking part in this project.

The research pathway can be visualized in a poster online. By following the arrows on the poster, the reader can follow the development of the research step by step, and understand the central role of the bibliography when a field is unknown [5].

This unexpected evolution made the database considerably more complex. The original model became unmanageable, necessitating a thorough overhaul. My son, a data engineer, lent his expertise, and we reconstructed the database fields from scratch. An undergraduate medical student assisted in repopulating the information in the new database. The

undertaking required considerable effort, as we currently have nearly 100 patients enrolled. To make sense of this vast dataset, a biostatistician friend of mine will assist in data analysis.

Initial Findings

The purpose of this brief paper is not to present an exhaustive set of results from the efforts but rather to illuminate the research journey. In this context, the path holds equal significance to the destination. It was previously inconceivable that primary care clinical practice could harness the cutting-edge technological advancements in transcriptomics or proteomics.

If the creation of the research pathway marks the first achievement, it's worth noting that, in the realm of imaging, SPECT-CT, which is more cost-effective and environmentally friendly than the 18FDG PET scan, allows us to observe alterations in cerebral perfusion in Long Covid. The outcomes of transcriptomic studies are exceptionally promising and will be the subject of a separate publication.

However, the most intriguing finding lies in the positive feedback from a majority of patients who feel understood and supported, even while acknowledging that their doctor is navigating uncharted territory with a new disease. These patients also prove to be invaluable research collaborators.

Deep suffering

Starting with a simple clinical observation, a question regarding a patient's recovery, my research journey has traversed various domains such as mixed research, transcriptomics, proteomics, neurobiology, and ontology. While it represents a fascinating realm of research, some call it translational [7], it is also intertwined with encounters with numerous individuals profoundly affected by this condition, underscoring the urgent need to find ways to alleviate their suffering.

Family medicine codes in the Core Content Classification of general practice ([3CGP](#)) : [A77](#); [QS41](#); [QR2](#) : [QR322](#) : [QR33](#)

Internet URLs

- Covid Human Genetic Effort : <https://www.covidhge.com/>
- Rega Institute, KUL, Leuven, Belgium : <https://rega.kuleuven.be>
- Brodin lab at Karolinska, Stockholm, Finland : <https://ki.se/en/neuro/brodin-laboratory>
- Neurobiology laboratory, University of Namur, Belgium : <https://www.unamur.be/medecine/urphym/lnr>
- Centre for Health Systems and Safety Research, Macquarie University, Sydney, Australia
<https://researchers.mq.edu.au/en/organisations/centre-for-health-systems-and-safety-research>
- HeTOP (Health Terminology/Ontology Portal), Rouen University, France. <https://www.hetop.eu/hetop/en>

Abbreviation

- SPECT-CT : single photon emission computer assisted tomography
- 18 FDG Pet scan : 18F-fluorodesoxyglucose positron-emission tomography/computed tomography
- Wonca : World organization of family doctors

Disclosure

- No conflict of interest
- Ethical agreement of the research obtained from Liege university and from Leuven University hospital ethical committees.

Sources

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Cher éditeur

Vous trouverez ci-joint le texte modifié.

Comme déjà souligné, j'ai été surpris par les commentaires du reviewer. Manifestement celui-ci a lu le texte comme un article de recherche. Je suis désolé de ne pas pouvoir répondre point par point à ces remarques pertinentes. Mais mon texte n'est définitivement pas l'exposé des résultats d'une recherche. Il s'agit de la description d'un chemin de recherche, ce qui est fort différent.

Je vous prie donc de bien vouloir présenter mes excuses au reviewer dont je comprends parfaitement les remarques.

J'ai donc modifié le titre et certaines parties du texte pour bien montrer que j'expose le chemin de recherche et non ses résultats.

Pour la bibliographie, j'ai choisi dans Zotero AMA 11th edition

En espérant que ce texte puisse correspondre à vos exigences éditoriales

Dear Editor

The amended text is attached.

As already pointed out, I was surprised by the reviewer's comments. I'm sorry I can't respond point by point to these pertinent remarks. My text is definitely not the results of a research project. It's a description of a search path, which is quite different.

Please accept my apologies to the reviewer, whose comments I fully understand.

So I've changed the title and some parts of the text to make it clear that I'm presenting the search path and not the results. For the bibliography, I have chosen Zotero AMA 11th edition I hope this text meets your editorial requirements.

Sincerely

MJ

