

Foreword

This article has been accepted for publication and undergone full peer review by The Permanente Journal. Due to the change in the patient's condition reported by the first author to the editor of The Permanente Journal, the editor decided to withdraw the article from publication. Family medicine has a fundamental characteristic called continuity of care. The continuity of the relationship with the patient will allow another article to be written that will contribute further to understanding the natural history of Long Covid

Please cite as; Jamouille M, Kazeneza-Mugisha G, Zayane A. Improvement of a Long Covid patient after vaccinations, a case report in family practice. e-print, Department of Family Medicine, University of Liege, Belgium, Jan 2022

Improvement of a Long Covid patient after vaccinations, a case report in family practice

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Abstract

Since 2019, primary care has been under great pressure from Covid-19 patients and now from those affected by Long Covid. The issue of this new condition, its diagnosis and available treatments, were investigated on the occasion of an anecdotal and unexpected recovery of a patient with Long Covid. A 48-year-old woman, a single mother of two and patient in our family practice for several years, became sick from Covid-19 in October 2020. She never recovered, and 9 months later was still showing signs of severe Long Covid with somatic, behavioral, cognitive and memory disorders. After her two vaccinations by Comirnaty - Pfizer/BioNTech, she reported severe side effects, followed at day 12 after the first vaccine by an unexpected improvement still present at day 30 and 44 of the Long Covid symptoms from which she had suffered for several months. SARS-CoV-2 antibodies were very high and although Magnetic Resonance Imaging were not very contributory, cerebral tomoscintigraphic examination was compatible with a cerebral pathology of vascular type. While no conclusions can be drawn from an isolated case, this case allows us to show that post Covid patients, who may already be highly comorbid, should be accompanied on a long-term basis. The disease is not yet precisely defined and symptoms may be non-specific

or may vary depending on the organs affected. Diagnostic procedures are not always helpful. A post Covid heartsink patient with medically unexplained symptoms may well be a Covid long hauler. This makes listening to the patient's words and narrative medicine very powerful.

Keywords: Long Covid; General Practice; Narrative Medicine; Vaccination, adverse effects; Recovery of Function

Key messages

- Long Covid is a new, multi-systemic, long-term condition that can be very debilitating.
- The main symptoms are intense fatigue, exertional exhaustion and cognitive and memory problems, among many others.
- Patients who suffer from it may not realize it, may not talk about it or may attribute their problem to other causes.
- There is yet no identified treatment that can be recommended. Careful listening, empathetic support and cognitive and physical rehabilitation are suggested.
- Research on this subject is burgeoning and several therapeutic avenues are being explored by researchers around the world.

1 Introduction; Long Covid in family medicine

Covid-19 is no longer just an acute disease. In a large number of previously infected patients, which can vary, according to the authors, from 10%¹ to up to more than 50%,² it can develop into a disabling disease, sometimes lasting several months, known as Long Covid.^{3,4,5} This denomination only first appeared in the literature in the summer 2020.^{6,7} Ruling Covid-19 in or out is still difficult as signs and symptoms have very poor diagnostic properties.⁸ Long Covid is equally really challenging to define⁹ and a Delphi study, led by the World Health Organization, has been necessary to reach a consensus.¹⁰ Long Covid is a multisystem disease, sometimes occurring after a relatively mild acute illness.¹¹ It encompasses distinct clusters of heterogeneous symptoms¹² that can overlap and evolve over time and are sometimes difficult to relate to Covid-19.^{13,14,15}

It is also the first disease defined by the patients themselves through social network exchange.^{16,17} The PubMed interface offers 59 citations in 2020, and 603 in 2021 as of Oct. 25, 2021 with the descriptors "post-acute

COVID-19 syndrome" [Supplementary Concept] OR "Long Covid" [TW]. Patient advocacy groups, of which many members identify themselves as long Covid cases, are also mobilizing through the Internet and social networks, for example in France (apresj20.fr), the United Kingdom (longcovidosos.org), the Netherlands (coronaplein.nu), Germany (longCoviddeutschland.org), Canada (covidlong-haulcanada.com) or the United States of America (survivorcorps.com). Long Covid support groups have appeared on Facebook, with several tens of thousands of members. All these patients willingly participate in online surveys, expressing many difficulties in being taken seriously.¹⁸

The Long Covid syndrome occurs in patients who are already often highly comorbid.¹⁹ They often have a hard time being heard²⁰ and are often labelled as *heartsink patients*.²¹ Long Covid can be highly disabling and is becoming a serious public health problem^{22, 23, 24, 25} with nearly one million people affected in the UK alone.²⁶ Long Covid refers to symptoms persisting for more than three weeks after the diagnosis, generally managed in general practice.²³ A state of unbearable fatigue, brain fog and myalgia are the most prevalent symptoms. The symptoms can be multiple and of varying intensity according to the areas of the body affected. Cognitive problems, memory and attention deficits, language dysarthria, behavioral frontal disorders, autonomic dysregulation, headaches, dyspnea, anosmia, dysgeusia, skin or digestive disorders, psychosocial distress, loneliness, anxiety, depression and sleep disorders have been related to Long Covid.^{27, 28, 29, 30, 1, 31} Long Covid should not be confused with the long-term consequences of severe Covid-19.³²

The absence of specific markers means that the diagnosis is based on the patient's word,²⁰ which is not without medico-legal consequences.³³ Only a Pet scan might provide precise information such as hypometabolism that affect some brain areas in some Long Covid with a strong neurological component.^{27, 34, 35} However, this process is not very accessible and is also expensive. Cerebral scintigraphy which is by contrast more accessible, can possibly show a disorder of cerebral blood perfusion in Alzheimer disease or stroke.³⁶ The reversibility of decreased neocortical glucose metabolism assessed by 18F- FDG PET/CT, accompanied by an improvement in cognitive functions may occur after 6 months in some patients.²⁴

There is no specific treatment although physicians could be valuable sources of support and explanation for these distraught and sometimes stigmatized patients.³⁷ Booklets such as the Leeds booklet for Covid patients are probably useful.³⁸ Psychotherapeutic care, neurocognitive

stimulation and physiotherapy seem to apparently bring some comfort^{39, 40} although the treatments are still controversial.⁴¹ Parkin et al. that propose “*an integrated multidisciplinary comprehensive model of care to deal with the growing number of cases*”.⁴² This formulation makes an interesting reference to the descriptions of the family physician’s job⁴³ who could very well become the manager of such an approach. There are no definitive, evidence-based recommendations for the management of post-acute COVID-19 as of yet; therefore, patients should be managed pragmatically and symptomatically.⁴⁴

When usual biological tests do not explain the fatigue or the symptoms towards a diagnosis,⁴⁵ the patient’s word remains. This is known as narrative medicine,⁴⁶ based on trust, expressed during a consultation between two people who have often known each other for a long time. Relational continuity⁴⁷ is one of the characteristics of general practice, and this continuity enables the family doctor to cope with multimorbidity and its attendant complexity.⁴⁸ One third of patients with post-Covid syndrome have pre-existing comorbidities.¹ Health inequalities are the rule in many countries and as stated by Berger et al., “*primary care providers are in a unique position to provide and coordinate care for vulnerable patients with Long Covid*”.⁴⁹

The family doctor is a natural interlocutor and will therefore be very well-placed to identify how Covid is not healing and that it is responsible for unexpected symptoms which overwhelm a patient, his relatives and employer who may not understand the situation. This empathetic relationship also allows the patient to present complaints that are not acceptable to them, such as exhausting fatigue or a previously unknown feeling of depression, which they will not dare to express to their family and which makes them fear the future.⁵⁰ A study among workers showed that many of them do not consult their doctor for this syndrome, and face social stigma when returning to work.⁵¹

It is important to take a careful history, to ask about an acute episode of Covid, and to have any symptoms and their timeline carefully detailed and noted, symptoms mild or severe which may affect all organs. It is also essential to assess cognitive disorders and psychological repercussions.⁵² A GP should not be surprised to hear a Long Covid patient saying; “*My body and I go our separate ways*”.

Underdiagnosing Long Covid could have dramatic consequences for the patients. If the patient feels very ill and a doctor don’t understand, the patient could become a case of medically unexplained symptom.⁵³ The

doctor could relate the issue to psychosomatic causes such as anxiety attack or to depression, which ultimately denies the patient's own experience.⁵⁴

A family doctor who is used to his patient will always be puzzled by a patient who is known to be athletic and healthy and who suddenly becomes exhausted and unable to carry out daily activities. In the same way, a mother who has never been ill and who suddenly becomes unable to look after her children and feels guilty about it cannot be labelled as depressed without further questioning.

From then on, only a meticulous narrative will exist to support the patient, first of all to identify and "name" the disease,⁵⁵ to justify it to himself, to his relatives, to his employer and to his insurer. For this tiring disease seems to have no end and no cure and moreover, as stated by Nath, is "*stigmatized as being functional*",⁴ a term usually used erroneously to deny the patient's experience. It is always difficult for a doctor to be put in a situation of failure. He/she feels him/herself reduced to listening and giving comfort when that is precisely what medicine is all about.

When a patient known to be very ill with Long Covid suddenly reports that she is well, the family doctor who follows her can only be surprised and curious to understand. It is an intellectual challenge to understand what happened and whether it can be replicated. In medicine and more particularly in general practice, each consultation can lead to a research process. To be confronted with such a question is a challenge. The case of unexpected improvement in a Long Covid after two vaccinations with Comirnaty Pfizer Biontech vaccine is reported and discussed in this article.

2 Methods

The setting is that of general practice, in Belgium, in a small group practice of family doctors working on a fee-for-service basis in a long-term relationship of trust with their patients, based on interpersonal continuity. The general practitioner (GP), for whom Covid burden has changed the professional practice by making it more accessible, particularly through remote consultation,⁵⁶ is the manager of the patient's information. This therefore ensures informational continuity⁵⁷ by the maintenance of a diagnostic index (list of problems) and a therapeutic index (list of medicines) as well as a daily journal.

A timeline which highlights key moments in the patient's development has been developed (Fig 1). The case has first been reported based on information from the medical records including an image of the cerebral scintigraphy (Table 1 & Fig 2). In order to complete the data and to have a more detailed view of the patient's experience according to the principles of narrative medicine,⁴⁶ two semi-structured interviews of the patient, on day 30 and day 44 after improvement, were conducted with a interview guide by one of the authors (GK), trainee in general practice. The patient is of Kurdish origin and understands French. The key sentences expressing her experience were extracted and translated into English (Table 2). The patient has given express permission in writing for the use of her medical data and the publication of the case.

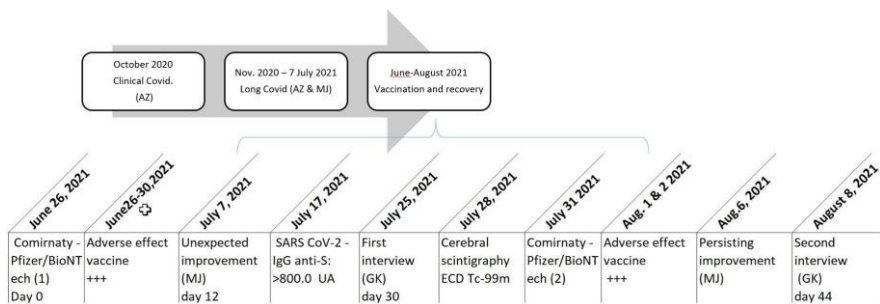


Fig. 1 Timeline ; Following acute Covid in October 2020 and 9 months Long Covid, unexpected improvement of the patient after the two Comirnaty vaccines which put the patient under great strain respectively 5 and 2 days. (AZ, MJ & GK: providers)

3 Result

July 7, 2021 was an unusual moment at the family practice of the Janson Medical Center. Mrs. B, a single 48-year-old mother with two children, without many resources and dependent on social support, has been a patient in the practice for several years. In October 2020 she had severe Covid for 3

weeks at home with dyspnea, sore throat, no fever, dysgeusia and a positive PCR test for SARS-CoV-2. Nine months later, she had not recovered. The patient was already known for tiredness due to minor thalassemia and occasional depressive feelings. However, her severe tiredness, headaches, dysgeusia, unusual depressive feelings, significant cognitive problems including omissions and loss of speech, put her in the Long Covid category without a doubt in light of the epidemic context. The last consultation had been difficult. She explained that she was crying a great deal, that her nights were haunted by strange hallucinatory dreams and that she could no longer cope.

Ongoing problems	Asthma - Common migraine - Domestic violence - Perimenopause - Pollen and dust mite allergy - Thalassemia minor -Urinary stress incontinence
Oct. 20; clinical Covid	Confirmed by PCR+, main symptoms; throat pain, rhinorrhea, achy ++, fatigue ++ and headache, but no breathing difficulties, dysgeusia , anosmia. Stay at home, cured after 12 days. PCR +. Home care only.
Nov. 20 - July 21: Long Covid,	Main symptoms ; pain in both eyes, ocular pruritus, rapid ocular fatigue, noise intolerance, memory loss (forgets to pick up her daughter at school), concentration problem, remains isolated in her room; dyspnea at the slightest effort and at speech; almost continuous osteoarticular and muscular pains, has become depressed, often with headaches. Dark circles around her eyes and swollen lower eyelids, easy crying that she doesn't understand, hallucinatory dreams, replaying past events (from ten years ago) and crying, she has the impression that she doesn't control what she thinks about. Suspected diagnosis; Long Covid with encephalitis. Brain MRI normal.
June 26, 21 Cerebral MRI	Minimal punctiform hyperintense Flair and left frontal subcortical T2 signal anomaly,
July 7,21 acute state post first vaccine	She got very sick after the vaccine Comirnaty - Pfizer/BioNTech (1st dose); she stays in bed for 5 days, she has pain everywhere, migraine, pain in her arm, she feels awful, she sleeps all the time, she has dizziness, inappetence, dysgeusia (the tea stinks). On the sixth day she is better. Today is the 12th day after the vaccination. She feels good, she is not tired anymore, she cleaned her house and she smiles. Lab test: SARS CoV-2 - IgG anti-S: >800.0 no abnormalities in the usual biology
July 28, 21 Cerebral scintigraphy	Tracer: ECD Tc-99m (Neurolite): Scintigraphic examination compatible with a cerebral pathology of vascular type with clearer vascular disorders left fronto-parietal, left frontal and left thalamic vascular disorders (Fig 2)
Aug. 6, 21. Second vaccine	Very seriously ill again after the second vaccination, but only for two days.(Extreme fatigue, headache, very cold without fever, nausea, very sick in bed) On the third day she can resume her life as a mother, goes shopping with her children, and starts laughing again. Considers herself cured of Covid. Still has memory problems.

Table 1 Notes from the EHR. The patient is a 48-year-old single woman with two children. Several comorbidities (see ongoing problems). Acute Covid, Long Covid and unexpected recovery after two Comirnaty vaccines

On June 26 she had her first dose of Comirnaty Pfizer Biontech vaccine. Twelve days later, she came for a consultation and the doctor expected to have to console and support her. But it was a smiling, happy woman who showed up. She explained that after the first jab she was immediately very, very ill with myalgia, headaches and loss of taste. She said her tea stank. The symptoms lasted five days during which she had to stay in bed. On the sixth

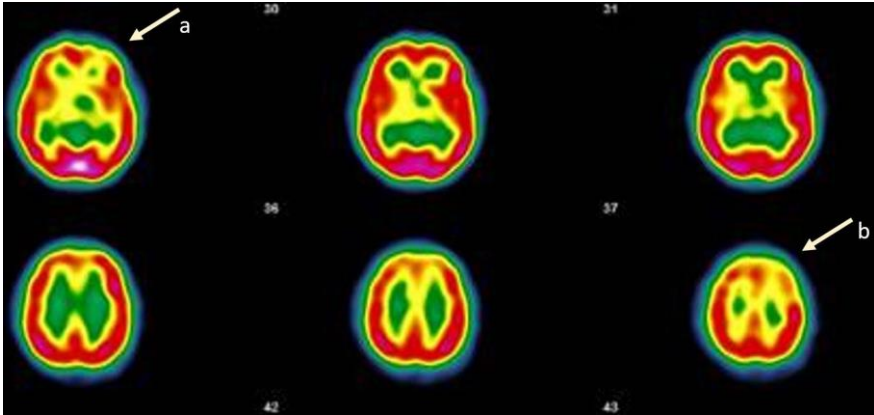


Fig. 2 The cerebral scintigraphy shows a hypofixation of the tracer in left cortico-frontal (a) and left fronto-parietal (b) areas. (Courtesy Drs Bouazza & Mahy, Vesale hospital, ISPPC, Belgium)

day, she woke up and felt alive again. Her abnormal tiredness, her depressive feelings and her headache had all disappeared. *"I am cured of everything"* she said with a smile.

Contacted by phone again ten days after, she confirmed that she had regained her good old thalassemic fatigue but was physically fit. She had been able to do her housework, care for her two children and clean her house. She was well, but still had some difficulty finding words. On July 31, the second dose of vaccine also caused a severe but shorter illness. The patient remained in bed for two days. On the third day, she got up feeling better, happy and smiling.

Minimal punctiform hyperintense FLAIR and left frontal subcortical T2 signal anomaly are seen on MRI. The usual laboratory tests showed no alterations. The anti-Sars-Cov2 antibody level was very high (800.0 UA/mL). Three weeks later, the cerebral tomoscintigraphic examination (ECD Tc-99m) was *"compatible with a cerebral pathology of vascular type with clearer left fronto-parietal, left frontal and left thalamic vascular disorders"* (Fig 2).

Two interviews conducted by one of the authors (GK) two weeks apart, made it possible to clarify the evolution of the Covid as well as the patient's experience and the various somatic and psychological problems she had to face (Table 2).

The acute Covid experience	<i>Before I got sick with COVID, I was generally feeling fine because I was used to my condition. But when I got Covid, everything became more difficult..." Before the Covid I was mentally pretty good, a little depressed but not much. But with Covid, I was at my lowest point. A week to ten days later, I became extremely sick and more and more afraid. I could hardly see, I couldn't even hold my phone. I felt like I had no oxygen left in my brain and I had to go to the window to breathe. I had awful headaches. I was thinking, 'I'm going to die, I'm going to die,' 'Why me? Why did I get the Covid?'. I wanted to die. Life seemed very dark to me, and I didn't feel like living, I didn't feel like eating. Even tea, which I usually like to drink, disgusted me. (...) For more than three weeks, I didn't eat, I lost weight, I couldn't sleep, I woke up at night, I cried and cried... I didn't know how to do anything.</i>
The Long Covid period	<i>For nine months I didn't laugh, I was always tired, I didn't go out, I was always in the chair. I had to eat all the time, I gained 7 kgs. I would have hunger attacks, and when I didn't eat, I would shake. In the morning, when I woke up, I ate, at night, I woke up and ate. Every morning I was waiting for the night to come and every night I waited for the morning. The days were endless because I was sick, I did nothing. I couldn't stand the TV or the noise. Before Covid, I thought I was a beautiful woman but when I looked at myself in the mirror, I said to myself "I am so old, as if I had aged ten years" I forgot a lot. Words, names. I had to repeat to myself "I must not forget, I must not forget". My brain was working backwards. I was angry for no reason. I was wondering "when will I die?"</i>
First Vaccine adverse effect	<i>My arm was sore and very heavy. I felt like I had 10 kilos on my arm. On the second day, I felt very sick and I was very tired [...] I slept at least 5 or 6 times in the same day: I drank a little water and then I went back to sleep,... For 5 or 6 days I slept a lot because I was very tired. I also had migraines, maybe because of my period? Maybe because of the vaccine? I don't know, I couldn't clean, I couldn't prepare food for my children".</i>
Day 12 post improvement	<i>I was cured of everything. I looked at myself in the mirror and I think I had changed: I was younger, I was a beautiful woman. Everything was gone... I don't know..., I was happy. So much so that I asked myself, "Doesn't the vaccine have a rejuvenating effect?". I explained to the doctor that I was much better after my vaccination and he was surprised. I always come to the doctor because I am not well, because I feel very sick, but here he was surprised and happy to see me in good shape. He told me that I was getting better and that I was going to beat Covid. So I was happy when I came home because I thought "I'm going to get well!"</i>
Day 30	<i>I felt good. I was breathing well, eating normally, sleeping well, happy. I had energy, but sometimes I forgot why I was doing this or that and I still had trouble seeing. I was a little less hard than before, but the difficulties were still there. The doctor told me it would pass, but we'll see</i>
Second Vaccine adverse effect	<i>The night after the second vaccination, I woke up at 3am, very sick. I was terribly cold, but the thermometer was only 35°Celsius. I had to put on hot water bottles. I had an incredible headache. I was sweating very hard. I was nauseous all day. This went on for two days. On the third day I woke up feeling good, made food for my children. I still had a bit of a headache, but I was well again.</i>
Day 44	<i>Today, I have no more problems. I'm a little tired and I have sciatica. I still have some forgetfulness for little everyday things, like not remembering why I go to a place but I do my shopping and I can count my money. However, I was more tired with the Covid than I am now. Now I'm fine. After the vaccination, I had my sciatica again. But now I want to say that Covid is over. Compared to Covid, sciatica is nothing. I've experienced sciatica before, so I don't care, but Covid, I'll never want to experience that again!</i>

Table 2 The patient was interviewed on days 12, 30 and 44 after improvement (GK). She is a Kurdish speaker expressing herself in French. The verbatim, translated in English, has been slightly improved.

4 Discussion

An anecdotal case that occurred during the follow-up of a patient on long-term Covid is reported here. The patient, during a family medicine consultation,

reported severe side effects after her vaccinations, followed by an almost complete recovery and a disappearance of most of the Long Covid symptoms from which she had suffered for several months. A month and a half after the vaccination, the patient was still having loss of words, but her condition has considerably improved despite persisting memory problems. The cerebral scintigraphy confirms the Covid vascular encephalopathy.

The relationship with the patient had been established for many years, and there is no reason to doubt that the patient had undergone a profound change in her condition. The answer to our communication from the Pfizer pharmacovigilance resource was very clear. Taking note of the report, they state that Comirnaty (COVID-19 mRNA Vaccine) is not indicated for the treatment of Long COVID symptoms.⁵⁸

Diagnosis process of Covid 19 is mainly clinical. Laboratory tests are not specific. PCR test could have been negative and serology, very positive in this case, is not always available and could be negative.³⁷ MRI can reveal cerebral microvascular injury in severe COVID-19^{59, 60} and cerebral scintigraphy could show perfusion anomalies in Alzheimer disease³⁶ but we have not been able to find a publication on its use in Covid 19. Positron emission tomography, whose interest in Covid is known^{35,24} is not available in primary care in Belgium. Perfusion anomalies, cognitive and memory problems could be explained by expression of ACE2 and other receptor by the brain vascular wall making them vulnerable to the virus.^{61,62}

The existence of Covid-related chilblains has made it possible to study in detail the immunological and vascular abnormalities of the skin.^{63, 64} One cannot help but think that what happens under the skin also happens in the cerebral vessels, bearing in mind that autopsy studies have identified SARS-CoV-2 RNA or protein in the brainstem of humans.⁶⁵ According to Wenzel et al, data show that SARS-CoV-2 infection induces a microvascular pathology in the brain in the form of string vessels. Overall, these data indicate that inhibitors of Receptor-interacting protein kinase 1 signaling may prevent cerebral microvascular pathology in COVID-19.⁶⁶

Prior COVID-19 infection appears to show significantly higher incidence and severity of self-reported side effects after a vaccination for COVID-19 as is the case in our patient.⁶⁷ It is suspected that non-related vaccination (like MMR) could enhance the innate response,⁶⁸ but as far as we know the effect of vaccination in a Long hauler has not been studied in depth. In a recent non-peer reviewed study, Strain et al. report that 57.9% of participants reported improvements in symptoms of Long Covid after vaccination while 17.9% reported deterioration.⁶⁹ A team of researchers at the Yale School of Medicine, led by immunologist Akiko Iwasaki and colleagues, has launched a study to determine the effect of vaccination on people with Long-Covid.⁷⁰

Weaker antibody responses has been shown in Long hauler.⁷¹ Mishra et al., investigating the immune responses at the level of B memory cells, refer to “a potential mechanistic explanation for the vaccination-induced reduction in symptoms in patients with Long COVID”.⁷² In 2020, Gaebler et al. stated that “the memory B cell response to SARS-CoV-2 evolves between 1.3 and 6.2 months after infection in a manner that is consistent with antigen persistence”.⁷³ Sekin and all showed that “T cells exhibited robust memory T cell responses months after infection, even in the absence of detectable circulating antibodies specific for SARS-CoV-2”.⁷⁴

It is therefore as if, in this particular patient, the persistence of the viral antigen is the cause of the symptoms of Long Covid and could hypothetically explain the severe adverse effect followed by positive effect of the vaccination. Given the limited knowledge on the natural course of Long Covid, it is not possible to draw any conclusions from this particular isolated observation. This unexpected recovery was worth reporting. However, anecdotes do not make medicine but they are by nature memorable and can serve to stimulate further research.⁷⁵ And indeed, the response to vaccination is the subject of a very detailed genetic international observational study on a population of Long Covid.⁷⁶ Global effort are performed to using genome sequencing to identify rare mutations that blunt the immune system’s normal defenses against the virus.⁷⁷

Post-viral chronic fatigue has been known for a long time and can follow both SARS,⁷⁸ influenza or Ricketts to name a few.⁷⁹ The placebo effect, the body’s natural defenses, and a patient’s own changes in life can all contribute to a patient’s apparent recovery if not complete, at least partial. Because mast cells (MC) are activated by SARS-CoV-2, mast cell activation syndrome (MCAS) has also raised interest in understanding why only some people suffer from it. This may pave the way for new therapeutic proposals.⁸⁰

This case study led to a continuous search of the most recent publications on Long Covid. Although research is abundant, there is still no solid and effective therapeutic proposal. The present paper therefore stresses the importance of both (1) Listening to the patient and sharing information between doctors, as well as (2) Maintaining trust with the patients which can lead to an efficient use of narrative medicine.

While no recommendations can be made from this isolated case and the vaccine certainly cannot be used for any purpose other than that for which it was officially designed, valuable information can be drawn from this. It should be borne in mind that no observation should be considered too small to be valid, yet these observations remain of little value unless they are exchanged with peers and subjected to careful analysis.

Conflict of interest

None

Ethics

The patient has expressly agreed in writing to the use of her personal data in an anonymous manner.

Acknowledgements

Ms Ondine Sherwood of LongCovidSOS (UK) was kind enough to give us some advice and to edit this manuscript in English. Her help was much appreciated.

A special thanks to Drs Salima Bouazza and Nathalie Mahy, specialist in nuclear medicine at the Vesale Hospital, ISPPC, Belgium for their availability and their very clear explanations.

Abbreviations

18-FDG PET CT: fluorine-18-fluorodeoxyglucose positron emission tomography

ACE2: angiotensin-converting enzyme 2

COVID-19 mRNA: COVID-19 ribonucleic acid messenger vaccine

ECD Tc-99m: Technetium-99m Ethyl Cysteinate Dimer

EHR : Electronic Health Record

FLAIR : Fluid-attenuated inversion recovery

GP: general practitioner

MCs : Mast cells

MCAS: Mast Cell Activation syndrome

MMR: Measles, Mumps and Rubella

MRI: Magnetic Resonance Imaging

PCR: Polymerase chain reaction

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

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