



ORIGINAL ARTICLE

# A retrospective analysis of clinically confirmed long post-COVID vaccination syndrome

Josef Finterer<sup>1\*</sup>, Fulvio A. Scorza<sup>2</sup>

<sup>1</sup>Neurology and Neurophysiology Center, Vienna, Austria, <sup>2</sup>Department of Neurological, Federal University of Sao Paulo Rua Pedro de Toledo, São Paulo, Brasil

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\*Corresponding author:

Josef Finterer

Neurology and Neurophysiology Center,

Vienna, Austria.

Email: [fifigs1@yahoo.de](mailto:fifigs1@yahoo.de)

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ABSTRACT

**Background and Aim:** Long post-COVID vaccination syndrome (LPCVS) is an increasingly recognized disease that occurs after SARS-CoV-2 vaccinations and lasts >4 weeks. However, little is known about the clinical presentation, underlying pathophysiology, treatment, and outcome of LPCVS. This study aims to present a series of patients with LPCVS, their treatment, and outcomes.

**Methods:** This was a retrospective analysis of three patients with LPCVS.

**Results:** In an observation period of 2 months (January and February 2022), three patients were collected in whom side effects after vaccination against COVID-19 lasted >4 weeks and in whom instrumental examinations were largely unremarkable. All three patients received only symptomatic therapy and only partially recovered within 6–8 months after vaccination. LPCVS significantly impaired the quality of life of the included patients.

**Conclusions:** SARS-CoV-2 vaccinations may cause not only short-term but also long-term side effects that include not only known diseases but also non-specific symptoms with normal or slightly abnormal clinical and instrumental findings. Although LPCVS leads to long-term disability, it is not widely recognized and not always accepted by manufacturers, health authorities, and even scientists. LPCVS should not be dismissed as a functional disorder and patients with LPCVS should be taken seriously.

**Relevance for Patients:** The possible causal relation between some long side effects and SARS-CoV-2 vaccines cannot be ignored. The pathophysiology of LPCVS should be further studied to lay a foundation for further improvement of the vaccines.

## 1. Introduction

It is well known that vaccinations against COVID-19 are not free from side effects in some patients [1]. Real world data have shown that these side effects can be mild or serious and can be short-lived or last for weeks or even months. Post-SARS-CoV-2 vaccination complications either include well defined diseases with abnormal findings on clinical examination and instrumental investigations (e.g., Guillain-Barre syndrome, venous sinus thrombosis (VST), and immune encephalitis), or one or more symptoms with or without abnormal findings on clinical examination or instrumental investigations. If side effects to SARS-CoV-2 vaccinations persist for >4 weeks with no or minimal abnormal findings on clinical or instrumental investigations, the condition is classified as long post-COVID vaccination syndrome (LPCVS) or long post-SARS-CoV-2 vaccination syndrome [2], in analogy to long-COVID-syndrome. We recently described a patient with LPCVS in whom clinical examination and instrumental investigations were negative [2]. Since then, a number of other patients with LPCVS and with or without abnormal instrumental findings

were reported. This study aims to present a series of patients with LPCVS, their treatment, and outcome.

## 2. Methods

Retrospectively, we evaluated the clinical and instrumental findings of three patients with LPCVS collected between 1/22 and 2/22. Parameters extracted from their records were age, sex, vaccine brand, number of doses after which LPCVS developed, latency between vaccination and onset of LPCVS, symptoms, signs and abnormal findings on instrumental examinations of LPCVS, treatment, and outcome.

## 3. Results

Three patients were included in the study (Table 1). Age ranged from 25 to 73 years. Two patients were male and one female. Two patients had received the Biontech-Pfizer vaccine and one had received the Moderna vaccine. LPCVS developed after the second injection in one patient and after the third injection in two patients. The symptoms were very variable and ranged from isolated and bilateral scintillating scotoma to unspecific multisystem manifestations (Table 1). The clinical examination was normal in one patient, showed only sore neck muscles in one patient, and generalized muscle soreness in the third patient. One patient had persisting Creatine-Kinase (CK) elevation but instrumental findings in the other patients were unrelated to vaccination. Two patients received analgesics, antidepressants, or muscle relaxants. One patient remained entirely without treatment. None of the patients experienced complete recovery during a follow-up of 6–8 months.

Patient-1 was a 25-year-old male with an uneventful history, who developed scotoma in the right eye for a few minutes shortly after the first dose of the Biontech-Pfizer vaccine. Shortly after the second stitch, he developed scintillating scotoma in both eyes, which persisted until the last follow-up 7 months after onset. Ophthalmological and neurological examinations were inconclusive. Visually-evoked potentials and magnetic resonance venography were non-informative.

Patient-2 is a 73-year-old male with a history of hyperlipidemia, diverticulosis, hypoacusis, cataract, and a solitary kidney cyst, who developed arterial hypertension, insomnia, and carpopedal spasms at rest and during exercise shortly after the three doses of the Moderna vaccine. Seven and 6 months previously, he had received the first and second doses of the Biontech-Pfizer vaccine and had bilateral, self-limiting gonalgia. The neurological examination only revealed sore neck muscles. The processing of his complaints was non-informative. He benefited from tizanidine and magnesium for insomnia and muscle cramps, but recovery was incomplete at the last follow-up 8 weeks after onset of symptoms.

The third patient is a 34 year-old female with a history of multiple allergies, who developed fever, myalgia, and severe fatigue a few hours after the second dose of the Biontech-Pfizer vaccine. Fever and myalgias resolved, but fatigability and exhaustibility remained unchanged over the next few months. After the third Biontech-Pfizer vaccine dose, 5 months after the second vaccination, she developed fever, myalgias, dizziness, dyspnea, and precordial pain. Immediate workup revealed elevated CK (1063U/l [n <170U/l]). The fever disappeared on metamizole and salbutamol, but the other symptoms remained unchanged until the last follow-up 2 months after the third injection.

## 4. Discussion

This case series shows that SARS-CoV-2 vaccinations can be complicated by side effects lasting >4 weeks (LPCVS) in single patients. Symptoms and signs of LPCVS are highly variable and may be associated with or without abnormal findings on instrumental examinations. LPCVS can occur at any age, in both sexes, and with any of the vaccine brands. Side effects of SARS-CoV-2 vaccines lasting >4 weeks include visual disturbances, myalgia, muscle cramps, fatigue, syncope, fever, headache, and palpitations. Clinical manifestations in the three presented patients were attributed to the vaccination because they were absent before vaccination and because of the temporal connection.

Long-term side effects of SARS-CoV-2 vaccines are increasingly recognized in the literature. One of the most common long-term side effects of SARS-CoV-2 vaccines, which has now been described in several hundred patients, is vaccine-induced immune thrombotic thrombocytopenia (VITT) [3,4]. It is estimated that VITT occurs in 0.5–1/100000 recipients of vector-based vaccines from AstraZeneca and Johnson and Johnson [5]. VITT cannot only be complicated by multilocular thrombosis but also by bleeding due to dysfunctional thrombocytes [6]. A 54-year-old male developed persisting VITT 12 days after the first dose of the AstraZeneca vaccine [6]. VITT was complicated by VST and recurrent intracerebral bleedings, which eventually led to a fatal outcome of the adverse reaction 4 months after vaccination [6]. In addition to VITT, several other long-term side effects have been reported. In a study of patients with SARS-CoV-2 vaccine-induced subacute thyroiditis, the median time to remission was 11.5 weeks [7]. An analysis of the WHO pharmacovigilance database (VigiBase) showed that the most common neurological side effects reported by patients to the database were ageusia, anosmia, burning sensation, dizziness, facial paralysis, headache, hypoesthesia, lethargy, migraine, neuralgia, paresis, parosmia, poor sleep quality, seizure, transient ischemic attack, and tremor [8]. These data are consistent with

**Table 1.** Patients with LPCVS included in the study

Age (y)	Sex	Brand	Dose	LVL	Symptoms	Signs	FII	Treatment	Outcome
25	m	BPV	2.	1	Scintillating scotoma	None	None	None	Persisting since 7m
73	m	MOV	3.	2	AHT, carpopedal spasms, episodic DV, pre-syncope	Sore neck	None	Trazodone	Persisting since 8w
34	f	BPV	3.	1	Fever, myalgia, fatigue	Sore muscles	CK ↑	Analgesics	Persisting since 2m

AHT: arterial hypertension, BPV: Biontech Pfizer vaccine, DV: double vision, f: female, FII: findings on instrumental investigations, LVL (days): latency between vaccination and onset of LPCVS, m: male, MOV: Moderna vaccine

the present investigations. Unfortunately, it was not reported how long these side effects lasted and whether they resolved spontaneously or only with treatment. In an observational survey of 379 patients carried out at the University of Texas, the most common side effects of SARS-CoV-2 vaccinations were found to be fatigue/tiredness, headache, myalgia, chills/fever, arthralgias, nausea, abdominal pain, diarrhea, rash, and vomiting [9]. As in the previous study, no information was given on the duration of these side effects. Another reported manifestation of LPCVS is chronic and spontaneous Urticaria (CSU) [10]. In a study of 27 patients with CSU after vaccination with the Biontech-Pfizer vaccine, multiple logistic regression analysis showed that a positive autologous serum skin test, allergic comorbidities, and basopenia were positively correlated with the likelihood of CSU recurrence within 3 months of the Biontech-Pfizer vaccination [10].

The pathophysiological mechanisms underlying LPCVS are unknown, but it is speculated that the immunologic response to viral RNA or viral proteins is responsible for each of these phenomena. Not only the SARS-CoV-2 virus, but also the various SARS-CoV-2 vaccines apparently trigger a strong immune response that lasts for weeks and leads to systemic compromise without severe abnormalities on clinical and instrumental examinations. An argument for the immunogenic hypothesis is that neither the spike protein nor mRNA particles have been detected in the CSF of patients developing side effects to SARS-CoV-2 vaccines [11].

## 5. Conclusions

This study shows that SARS-CoV-2 vaccines cause not only short-term but also long-term side effects in some patients that long-term side effects include not only definite diseases, but also non-specific symptoms with normal or slightly abnormal instrumental findings and that the quality of life is significantly reduced by these side effects. Since LPCVS is not widely recognized and not widely accepted by manufacturers, health authorities, and even scientists, further studies are needed to confirm the causal relation between vaccination and LPCVS, to discover the underlying pathophysiology of LPCVS and to develop effective therapies. LPCVS should not be dismissed as a functional disorder and patients with LPCVS should be taken seriously.

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## Conflicts of Interest

The authors declare no conflicts of interest.

## Ethics Approval and Consent to Participate

The approval was in accordance with ethical guidelines. The study was approved by the institutional review board. Consent to participate was obtained from the patients.

## Consent for Publication

Consent for publication was obtained from the patients.

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