

Neurological side effects of SARS-CoV-2 vaccinations

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SARS-CoV-2 and adverse reactions to SARS-CoV-2 vaccinations show a tropism for neuronal structures and tissues. This narrative review was conducted to collect and discuss published data about neurological side effects of SARS-CoV-2 vaccines in order to discover type, frequency, treatment, and outcome of these side effects. The most frequent neurological side effects of SARS-CoV-2 vaccines are headache, Guillain-Barre syndrome (GBS), venous sinus thrombosis (VST), and transverse myelitis. Other neurological side effects occur in a much lower frequency. Neurological side effects occur with any of the approved vaccines but VST particularly occurs after vaccination with vector-based vaccines. Treatment of these side effects is not at variance from similar conditions due to other causes. The worst outcome of these side effects is associated with VST, why it should not be missed and treated appropriately in due time. In conclusion, safety concerns against SARS-CoV-2 vaccines are backed by an increasing number of studies reporting neurological side effects. The most frequent of them are headache, GBS, VST, and transverse myelitis. Healthcare professionals, particularly neurologists involved in the management of patients having undergone SARS-CoV-2 vaccinations, should be aware of these side effects and should stay vigilant to recognize them early and treat them adequately.

KEYWORDS

adverse reaction, COVID-19, neuropathy, SARS-CoV-2, side effect, vaccination

1 | INTRODUCTION

Though SARS-CoV-2 vaccinations are usually sold as well tolerated, they can cause mild-to-severe side effects in some patients.¹ Since the benefit for the global population outweighs these adverse reactions, and since political and pecuniary interests create the image of a “safe and indispensable” tool against the currently dominant global burden, there is only moderate reporting and discussion about them.² There is also an anti-vaccine movement in the world nowadays that also contributes to the biased assessment of these adverse effects. Usually, single case reports, case series, or registration studies report these side effects but systematic, transnational, multicenter, post-marketing investigations on this matter are infrequently done. This shortage of published information about type, frequency, severity, and therapeutic management of vaccination-related side effects is

in contradiction to the daily experience of healthcare workers and affected probands, and may contribute to the individual or organized resistance and reservations against the vaccination from parts of the populations, the only moderate effect of vaccination campaigns, and the tendency to introduce compulsory vaccination.³

Neurological side effects to SARS-CoV-2 vaccinations are usually mild, of short duration, self-limiting, and ambulatorily manageable. However, in some cases, these side effects are severe and require hospitalization or even admission to an intensive care unit (ICU).⁴ Only, rarely these side effects can be fatal.⁵ Since the virus and the adverse reactions to vaccinations show a tropism for neuronal structures and tissues this narrative review about the neurological side effects was conducted to collect and discuss published data in order to discover type, frequency, treatment, and outcome of these side effects and to eventually discover if certain patients are prone to

experience them, if they can be prevented, and which therapeutic management is the most appropriate.

2 | METHODS

A literature search in the databases PubMed and Google Scholar using the search terms “vaccination”, “SARS-CoV-2,” “anti-covid vaccination,” “immunisation” in combination with the terms “side effects,” “adverse reactions,” “neurological,” “brain,” and “nerves” was conducted for the period December 2020 to September 2021. Initially detected were 62 titles in PubMed and 4580 in Google Scholar. Most of them were excluded already after having read the title or the abstract. Included were only original articles which convincingly reported a neurological adverse reaction. Excluded were articles which were repetitive and articles in which a causal relation between the vaccination and the complication could not be convincingly established. Additionally, reference lists were checked for further articles meeting the search criteria. All approved vaccines were considered. Lastly, 28 papers were included.

3 | RESULTS

Neurological side effects of SARS-CoV-2 vaccines collected from the literature are listed in Table 1. They include headache, Guillain-Barre syndrome (GBS), venous sinus thrombosis (VST), transverse myelitis, facial nerve palsy, small fiber neuropathy, newly developing multiple sclerosis, and some others that have been reported only in a few patients (Table 1). By far the most frequent of the neurological adverse reactions to SARS-CoV-2 vaccinations is headache, followed by GBS, VST, and myelitis (Table 1). Neurological side effects develop after any of the commercially available anti-COVID-19 vaccines but myelitis predominantly after application of the AstraZeneca vaccine (AZV).

In a recent multinational, multicenter observational cohort study by means of a standardized questionnaire, among inhabitants of residential care homes of the elderly and patients from hospitals, 2349 patients reported headache after vaccination with the Pfizer vaccine.⁶ Headache started on the average 18 h after the shot and lasted on the average for 14 h.⁶ In two thirds of these cases, headache manifested with a single episode. In 38% and 32% of the cases, headache occurred in a frontal or temporal distribution, respectively.⁶ Headache was characterized as dull in 40%, and intensity was very severe in 8.2%, severe in 32.1%, and moderate in 46.2%.⁶ According to one of the registration studies for the AZV, headache was the most frequent neurological complication of SARS-CoV-2 vaccinations without providing an exact figure of the headache frequency.⁷ In a study of 1480 healthcare workers from Malta undergoing vaccination with the Pfizer vaccine, 655 probands reported headache after the first or second shot.⁸ Several other studies evaluated the frequency of side effects, why the true figure about headache frequency probably exceeds that provided in Table 1.

In a recent review about Guillain-Barre syndrome (GBS) following a SARS-CoV-2 vaccination, 19 cases were collected as per the end of July 2021.⁴ Fifteen patients had received the AZV, four patients the Pfizer vaccine, and 2 the Johnson & Johnson vaccine.⁴ In six of these patients, respiratory muscles were involved why they required mechanical ventilation. Only in a single patient was complete recovery achieved until the last follow-up under standard GBS therapies.⁴ All other patients in whom the outcome was reported achieved only incomplete recovery. One of the 19 patients had a history of a previous GBS from which he had completely recovered.¹ Recently, a further case with post-vaccination GBS after having been vaccinated with the AZV has been reported.⁹ This patient remained bedridden by the 4-week follow-up.⁹

Thrombotic events in cerebral veins are another neurological complication of SARS-CoV-2 vaccinations. VST has been most frequently reported after vaccinations with the AZV.¹⁰ In most cases, VST occurred already after the first shot. Patients in whom VST was attributed to immune-mediated thrombocytopenia received IVIGs or steroids in addition to heparin.¹⁰ Notably, sixty-two patients with post-SARS-CoV-2 vaccination VST died.¹⁰ In the study with the highest number of patients experiencing a VST after shots with the AZV ($n = 187$), Pfizer ($n = 25$), or Moderna ($n = 1$) vaccine, concomitant thrombocytopenia was found only among those having received the AZV.¹¹ Of the 117 patients with a reported outcome, 44 (38%) in the AZV group had died, compared to 20% in the Pfizer/Moderna group.¹¹

The fourth most frequent neurological side effect of SARS-CoV-2 vaccinations is transverse myelitis, which has been reported in 11 patients so far (Table 1). In seven of them, transverse myelitis occurred after application of the AZV (Table 1). In the patient having received the Johnson & Johnson vaccine, transverse myelitis was associated with facial palsy.¹² The patient who developed transverse myelitis after vaccination with the Moderna vaccine, additionally had vitamin-B12 deficiency, which may have contributed to the development of the neurological compromise.¹³

Several other neurological abnormalities occurred after SARS-CoV-2 vaccinations, but the number of reported cases was below 5 (Table 1). Facial palsy, for example, was reported in four patients and usually occurred unilaterally but occasionally bilaterally.^{14,15} Among the cases so far reported, facial palsy occurred as an isolated condition without being associated with other neurological compromise. We did not include “myalgia” as it is only a symptom and usually the underlying diagnosis is unknown.

4 | DISCUSSION

This narrative review shows that the most frequent neurological side effects of SARS-CoV-2 vaccines are headache, GBS, VST, and transverse myelitis. Other neurological side effects occur in a very low frequency as expressed by a number of published cases <5. The worst outcome of these side effects is associated with VST, why it should not be missed and treated appropriately in due time.

TABLE 1 Neurological side effects of SARS-CoV-2 vaccines as per the end of September 2021

NAR	NOP	Vaccine type	Outcome	Reference
Headache	3051	AZV, Pfizer	CR	6,7
GBS	389	AZV, Pfizer, JJ	CR, PR	4,9
VST	312	vector-based, AZB, JJ	nr	16,17
Transverse myelitis	11	AZV, Moderna, JJ Sinovac	PR, CR, nr	12,13,19-26
Facial nerve palsy	4	AZV, Pfizer Bharat Biotech	CR, PR	15,20,27 14
Small fiber neuropathy	3	Moderna, Pfizer	CRm PR, nr	28
Autoimmune encephalitis	3	ATV	PR	29
RCVS	2	Moderna	CR	[Personal communication]
Multiple sclerosis	2	Moderna, Pfizer	nr	30
Neuromyelitis optica	2	Pfizer, vector based	CR	30,31
Ischemic stroke	1	AZV	PR	20
ICB	1	Pfizer	PR	32
Tolosa-Hunt syndrome	1	nr	PR	33
Hypophysitis	1	Moderna	CR	34
Epilepsy	1	Moderna	CR	35
Hyperactive encephalopathy	1	Moderna	PR	36
ADEM	1	Pfizer	PR	37

Abbreviations: ADEM, acute disseminated encephalomyelitis; AZV, AstraZeneca vaccine; CR, complete recovery; ICB, intracerebral bleeding; JJ, Johnson & Johnson vaccine; NAR, neurological adverse reaction; nr, not reported; PR, partial recovery; RCVS, reversible cerebral vasoconstriction syndrome; VST, venous sinus thrombosis.

Headache is by far the most frequent neurological side effect of SARS-CoV-2 vaccinations and occurs with any of the approved vaccines. In the majority of cases, headache starts within a few hours after the vaccination and resolves spontaneously within 48 h.⁶ However, a subacute type of headache has been delineated which occurs on the average 8 days after the shot and is frequently associated with VST.¹⁶ The cause of headache after SARS-CoV-2 vaccinations remains speculative but generally, it can be tension-type headache due to stress, due to intracerebral bleeding (ICB) or subarachnoid bleeding (SAB), due to vasospasms like in SAB or reversible, cerebral vasoconstriction syndrome (RCVS), or due to VST. As VST is frequently associated with ischemic stroke, ICB, or SAB,¹⁷ headache may be multi-causal in patients experiencing VST. Thunderclap headache typically occurs with SAB or RCVS.

The pathophysiological mechanism of GBS post-SARS-CoV-2 vaccination is poorly understood but molecular mimicry is regarded as the most plausible concept. Considering that SARS-CoV-2 vaccines induce immunization against the spike protein and that the SARS-CoV-2 spike protein can bind to sialic acid-containing glycoprotein and gangliosides on cell surfaces, an antibody cross-reaction may be the most likely causal link between GBS and immunization to SARS-CoV-2.⁹

Venous sinus thrombosis is the third most frequent complication of SARS-CoV-2 vaccinations and explained by hypercoagulability. Hypercoagulability after a SARS-CoV-2 vaccination has been attributed to activation of platelets by the virus or to enhancement of the coagulation system by indirect activation of endothelial cells by SARS-CoV-2, shifting endothelium from an anti-thrombotic to a pro-thrombotic state, and by direct activation of complement pathways, promoting thrombin generation.¹⁸

A limitation of the review is that not all patients experiencing side effect may have been included. Patients with side effects may have been missed simply because the side effects were mild and not worth to be reported. It is also conceivable that not each patient with a presumed side effect was also published, as publishing is time-consuming and increasingly expensive.

In conclusion, this study shows that safety concerns against SARS-CoV-2 vaccines are backed by an increasing number of studies reporting neurological side effects. The most frequent of them are headache, GBS, VST, and transverse myelitis. Healthcare professionals, particularly neurologists, involved in the management of patients having undergone SARS-CoV-2 vaccinations, should be aware of these side effects and should stay vigilant to recognize them early and treat them efficiently.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

JF: literature search, discussion, first draft, critical comments, and final approval.

ETHICAL APPROVAL

The study was approved by the institutional review board.

INFORMED CONSENT

Informed consent was obtained.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ane.13550>.

DATA AVAILABILITY STATEMENT

All data used for the review are available from the corresponding author.

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