Review
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Neurological Adverse Reactions to SARS-CoV-2 Vaccines

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SARS-CoV-2 vaccines are not free of side effects and most commonly affect the central or peripheral nervous system (CNS, PNS). This narrative review aims to summarise recent advances in the nature, frequency, management, and outcome of neurological side effects from SARS-CoV-2 vaccines. CNS disorders triggered by SARS-CoV-2 vaccines include headache, cerebro-vascular disorders (venous sinus thrombosis [VST], ischemic stroke, intracerebral hemorrhage, subarachnoid bleeding, reversible, cerebral vasoconstriction syndrome, vasculitis, pituitary apoplexy, Susac syndrome), inflammatory diseases (encephalitis, meningitis, demyelinating disorders, transverse myelitis), epilepsy, and a number of other rarely reported CNS conditions. PNS disorders related to SARS-CoV-2 vaccines include neuropathy of cranial nerves, mono-/polyradiculitis (Guillain–Barre syndrome [GBS]), Parsonage–Turner syndrome (plexitis), small fiber neuropathy, myasthenia, myositis/dermatomyositis, rhabdomyolysis, and a number of other conditions. The most common neurological side effects are facial palsy, intracerebral hemorrhage, VST, and GBS. The underlying pathophysiology is poorly understood, but several speculations have been generated to explain the development of CNS/PNS disease after SARS-CoV-2 vaccination. In conclusion, neurological side effects develop with any type of SARS-CoV-2 vaccine and are diverse, can be serious and even fatal, and should be taken seriously to initiate early treatment and improve outcome and avoid fatalities.

KEY WORDS: Side effects; COVID-19 vaccination; Neurological; Brain; Nerves.

INTRODUCTION

It is now undisputed that SARS-CoV-2 vaccines not only have positive but also negative effects, i.e., side effects (adverse reactions) [1,2]. Side effects can be mild, moderate, severe, or fatal [1,2]. Side effects occur with all currently marketed vaccine brands (Table 1), but the spectrum and frequency of side effects may differ slightly between brands [2]. Side effects occur after any dose, in both sexes, and with variable latency after vaccination. A causal relationship is considered established if side effects occur within four [1] to six [3,4] weeks after vaccination. Side effects can affect any organ or tissue, but the most commonly affected organ is the central or peripheral nervous system (CNS, PNS) [1]. Various CNS/PNS disorders have been attributed to SARS-CoV-2 vaccines, but the causal relationship often remains unproven. This narrative review aims to summarise recent advances and future perspectives regarding the nature, frequency, management, and outcome of side effects from SARS-CoV-2 vaccinations (SC2Vs).

METHODS

A literature search in the databases PubMed, Google Scholar and Scopus was conducted using the search terms “SARS-CoV-2”, “COVID-19”, “vaccination”, and “immunisation”, in combination with “complication”, “side effect”, “adverse reaction”, “central nervous system”, “peripheral nervous system”, “brain”, “nerve”, “neurological”, “encephalitis”, “meningitis”, “stroke”, “bleeding”, “venous sinus thrombosis”, “multiple sclerosis”, “acute disseminated encephalomyelitis”, “seizure”, “Guillain Barre syndrome”, “Parsonage Turner syndrome”, “myositis”, and “myasthenia”. In addition, reference lists were searched for additional articles that matched the search criteria.

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Table 1. Most common marketed anti-SARS-CoV-2 vaccines

Company	Generic name	Brand name®	Technology	Number of dosages
Biontech Pfizer	BNT162b2	Comirnaty	m-RNA	Two/booster
Moderna	m-RNA1273	Spikevax	m-RNA	Two/booster
Astra Zeneca	ChAdOx1-S nCoV-19	Vaxzevira	Viral vector	Two/booster
Curevac	CVnCoV	Zorecimeran	m-RNA	Two
Novavax	NVX-Cov2373	Novaxovid	Protein subunit	Two
Johnson & Johnson	Ad26.COV.2S	Jcovden	Viral vector	One
Sinovac	CoronaVac	CoronaVac	Viral vector	Two/booster
Valneva	VLA2001	COVID-19 vaccine	Viral vector	Two/booster
Sinopharm	COVID 2019 vaccine	BIBP	Viral vector	Two/booster
Gam-Covid-Vac	Sputnik-V	Gam-Covid-Vac	Viral vector	Two
Bharat Biotech	BBV152	Covaxin	Viral vector	Two/booster
CanSino Biologics	Ad5-nCoV	Convidecia	Viral vector	Single
Sinopharm	BBIBP32-CorV	Covilo	Viral vector	Two booster
Sanofi Pasteur	VidPrevtyn beta	VidPrevtyn beta	Protein subunit	One

Original articles and reviews published between 1966 and December 2022 were included. Abstracts, proceedings, and editorials were excluded from data analysis. The review does not claim to be complete, since the number of words and references was necessarily limited.

RESULTS

In most studies female preponderance of neurological side effects was reported [3]. In a study of 60 patients with venous sinus thrombosis (VST) due to a SC2V, 75% were female. According to a multicentre study on 4,478 healthcare workers from Sri Lanka, low age and female sex were associated with an increased frequency of developing systemic reactions to vaccination with the Astra Zeneca vaccine (AZV) [5].

CNS Diseases Complicating SC2Vs

CNS disease reported as side effects of anti-SC2Vs are listed in Table 2 [4,6-129]. SC2V-related CNS disease includes headache, cerebrovascular disease, inflammatory disorders, epilepsy, and other conditions. Additionally, CNS diseases due to side effects manifesting in extra-neural tissues (e.g., myocarditis or vaccine-induced, immune thrombotic thrombocytopenia [VITT]) have to be taken into account.

Headache

Headache is one of the most common neurological side effects of SARS-CoV-2 vaccines. Headache has been reported in 30−51% of vaccinees [2,5]. According to a multicentre study on 4,478 healthcare workers, 50.8% developed transient headache after vaccination with the AZV [5]. In a study of 13,809 vaccinees experiencing neurological side effects, 30% reported headache [2]. Headache usually occurs within a few hours after vaccination and lasts either for a few hours or for several days. If headache persists for longer, diseases of the CNS, PNS, ears, eyes, or of the cardiovascular system should be considered. SC2V-related headache can go along with or without an identifiable cause [6]. Identifiable causes of headache include arterial hypertension, vasospasm, intracerebral hemorrhage (ICH), subarachnoid bleeding (SAB), reversible, cerebral vasoconstriction syndrome (RCVS), autoimmune encephalitis (AIE), aseptic meningitis, giant cell arteritis (GCA), pituitary apoplexy, VST, or cranial nerve neuralgia [6]. In the majority of cases, however, the cause of post-vaccination headache remains elusive. Headache has been reported with any brand of SARS-CoV-2 vaccines. A 21-year-old female experienced thunderclap headache with nausea, and vomiting 8 hours after the first AZV dose [7]. All investigations for specific causes of headache were non-informative [7]. No cause of recurrent thunderclap headache could be detected also in a 62-year-old female after a Biontech Pfizer vaccine (BPV) dose [7]. Headache after a SC2V may also derive from apoplexy of a pituitary adenoma [8]. A 50-year-old male experienced nausea, vomiting, diplopia, and drug-resistant headache one day after the third Moderna vaccine (MOV) dose [8]. Pituitary magnetic resonance imaging (MRI) revealed bleeding inside a macro-adenoma, consistent with pituitary apoplexy [8]. In patients with known migraine

Table 2. Mild, moderate, and severe CNSside effects of SARS-CoV-2 vaccinations

CNS disorder	Frequency	Reference
Cerebrovascular diseases		
Venous sinus thrombosis	+++	[108]
Ischemic stroke	+++	[14]
Transitory ischemic attack	+	[20]
Intracerebral hemorrhage	+++	[22]
Subarachnoid bleeding	+	[31]
Vasculitis		
Giant cell arteritis	++	[4]
AAION	+	[39]
Pituitary apoplexy	+	[43]
Reversible, cerebral vasoconstriction syndrome	+	[16]
Susac syndrome	+	[45]
Inflammatory diseases		
Encephalitis		
Non-specific encephalitis	++	[46]
Limbic encephalitis	+	[4]
Rhombencephalitis	+	[57]
ANE, AHNE	+	[58]
ADEM	++	[71]
AHEM	+	[74]
Multifocal necrotising encephalitis	+	[76]
Cerebellitis	+	[77]
Meningitis (aseptic, MEWDS)	+	[78]
Demyelinating disorders		
Multiple sclerosis (flair/new onset)	+	[81]
Cerebral isolated syndrome	+	[81]
Optic neuritis	+	[68]
NMO-spectrum disorders	+	[84]
MOGAD	+	[83]
Transverse myelitis	+	[109]
Epilepsy		
Due to VST, encephalitis, stroke etc.	++	[56]
Without evident trigger or structural lesion	++	[93]
Others		
Opsoclonus myoclonus syndrome	+	[48]
Narcolepsy	+	[94]
Tolosa Hunt syndrome	+	[110]
Cytotoxic lesion of the corpus callosum	+	[111]
Neuroleptic malignant syndrome	+	[112]
Hypophysitis	+	[113,114]
Wine glass sign	+	[2]
Idiopathic intracranial hypertension	+	[115]
ACTH deficiency	+	[116]
Tremor	+	[20]
Secondary due to coagulopathy, cardiac disease, superinfections		
VITT	+++	[117]
Myocarditis	+	[76]
Ramsay Hunt syndrome	+	[118]
Hemorrhagic encephalitis	+	[110]
Zoster (exacerbation) infections	+	[96]
SCLS	+	[93]

+, rare; ++, repeatedly reported; +++, common; CNS, central nervous system; AAION, arteritic, anterior, ischemic optic neuropathy; ANE, acute, necrotizing encephalopathy; AHNE, acute, hemorrhagic necrotizing encephalopathy; ADEM, disseminated encephalomyelitis; AHEM, acute, hemorrhagic encephalomyelitis; MEWDS, multiple evanescent white dots syndrome; NMO, neuromyelitis optica; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; VST, venous sinus thrombosis; ACTH, adeno-corticotropic hormone; VITT, immune thrombotic thrombocytopenia; SCLS, systemic capillary leak syndrome.

SARS-CoV-2 vaccines can increase the frequency of attacks or trigger new clinical manifestations. In a study of eight patients with a history of migraine focal neurological deficits (lateralised sensory disturbances, motor deficits, or both) developed within 24 hours after SC2V and lasted 2−14 days. Migraine occurred in four of them [9]. Because cerebral MRI was normal and single photon emission computed tomography studies showed large regions of hypoperfusion and small regions of hyperperfusion, neurological deficits were interpreted as migraine aura [9]. SC2V-related headache responds favourably to non-steroidal, anti-rheumatic drugs (NSARs), opioids, or opiates.

Cerebrovascular diseases

SC2V-related cerebrovascular diseases include VST, ischemic stroke, ICH, SAB, pituitary apoplexy, RCVS, cerebral vasculitis, and Susac syndrome (Table 2) [4,6-129].

Venous sinus thrombosis

VST is one of the most common and most severe CNS complications of SC2Vs but the prevalence of VST may vary significantly between studies. In a review of 86 articles about neurological side effects of SC2Vs, VST was reported in 706 patients [2]. However, in a study of 232,603 vaccinees, SC2V was complicated by VST in only three cases [3]. VST was first described in July 2021 in two males who developed fatal VST following the first AZV dose [10]. Meanwhile, several hundred cases of SC2V-related VST have been reported. VST manifests commonly with focal neurological deficits, seizures, and a dip in sensorium. VST can be associated by venous and arterial thrombosis in vascular beds other than the cerebral vasculature. VST may occur with or without VITT. VITT is due to IgG antibodies directed against the platelet factor-4 (PF-4) polyanion complex located on the surface of thrombocytes but additionally bind to un-complexed PF-4. These antibodies activate thrombocytes, resulting in platelet aggregation, hyper-coagulation and thrombocytopenia. Intravenous immunoglobulins (IVIGs) and non-heparin-based anticoagulation are the mainstay of treatment for VITT [11]. Second dose/boosters of mRNA COVID-19 vaccines appear safe in patients with adenoviral vector-associated VITT [11]. The cause of VST in patients without VITT remains elusive. The outcome of VST due to VITT also varies considerably between studies. In a retrospective study of 36 patients with VST due to VITT, the outcome of SC2V-related VST was fatal in up to 40% of cases [12].

Ischemic stroke

There is increasing evidence that SC2Vs can be complicated by acute ischemic stroke [13]. The prevalence of ischemic stroke, however, varies considerably between studies [13]. In a meta-analysis of 782,989,363 vaccinees, acute ischemic stroke was reported in 17,481 of them [14]. The pooled proportion of SC2V-related ischemic stroke amounted to 4.7 cases per 100,000 vaccinations [14]. In a retrospective study of Mexican vaccinees receiving six different types of vaccines between 12/2020 and 8/2021, acute ischemic stroke was found in 0.54 per 1,000,000 doses (95% confidence interval [CI] 0.40−073) [15]. The pathophysiology of ischemic stroke after SC2V is poorly understood but it is speculated that it is due to vasculopathy (arterial hypertension, endotheliali-tis, vasculitis, vasospasms, dissection), coagulopathy (cardioembolism, dysfunctional thrombocytes [e.g., VITT]), VST, or cardio-embolism (endocarditis, myocarditis, intraventricular thrombus formation, atrial fibrillation). A few patients have been reported who developed RCVS time-linked to a SC2V, manifesting clinically with severe headache and consecutive ischemic stroke [16]. In a 60-year-old female occlusion of the right internal carotid artery due to VITT seven days after the first AZV dose resulted in fatal stroke in the territory of the right middle cerebral artery (MCA) and anterior cerebral artery [17]. There was thrombocytopenia of 5,000 per µl and PF-4 antibodies were positive [17]. Treatment of SC2V-related ischemic stroke is not at variance from treatment of stroke not associated with SC2V except for stroke due to VITT. Patients with SC2V-related ischemic stroke may benefit from thrombectomy or thrombolysis as patients with stroke due to other causes [18]. A 83-year-old Japanese female with long-term atrial fibrillation and anticoagulation with rivaroxaban experienced occlusion of the left MCA three days after the first BPV dose but recovered almost fully after systemic thrombolysis and thrombectomy [19]. Three days after the second BPV dose she suffered occlusion of the right MCA but thrombectomy was unsuccessful this time [19]. Several patients with a transitory ischemic attack shortly after SC2V have been reported [20].

Intracerebral bleeding

SC2V-related ICH with or without breakthrough to the ventricles or the subarachnoid space is not infrequent. In a review of 86 articles about the neurological side effects of SC2Vs, 2,412 patients with ICH were listed [2]. In a retrospective study of vaccinees receiving 79,399,446 doses of six different SARS-CoV-2 vaccines, ICH was reported in nine patients (16.1%, 0.11 per 1,000,000 doses (95% CI 0.06−0.22) [15]. The outcome was favourable with a modified Rankin scale of 0−2 in 41.1% of cases but fatal in 21.4% [15]. SC2V-related ICH can be generally due to arterial hypertension or hypocoagulability (VITT). SC2V-related ICH is more commonly associated with than without VITT. SC2V-related ICH usually manifests as macro-bleeding. Microbleeds have been only rarely reported. In a 57-year-old female, ICH occurred five days after the first AZV dose. Digital subtraction angiography ruled out aneurysm or occlusion and platelet counts were normal. Because she had taken acetyl-salicylic acid for general malaise immediately after vaccination, ICH was attributed to the antithrombotic effect of the drug [21]. VITT-associated ICH was reported in a 60-year-old female who suffered fatal right frontal lobar ICH 16 days after the first AZV jab [22]. There was only moderate thrombocytopenia but PF-4 antibodies were elevated [22]. In a 40-year-old female with Moyamoya disease, Sjögren syndrome, and autoimmune thyroiditis, application of the second MOV dose was complicated by left ICH and intraventricular bleeding 3 days after SC2V [23]. The patient benefited from an external ventricular drainage and subsequent stereotactic evacuation of the hematoma [23]. A 46-year-old female developed ICH due to vasculitis following the first BPV dose [24]. The patient benefited from surgical evacuation of the clot [24]. Several other cases of SC2V-related ICH have been reported [25-30].

Subarachnoid bleeding

SAB is a rare complication of SC2Vs. It usually occurs in patients who experience VITT with consecutive VST but without an aneurysm. A 48-year-old male developed hematuria, petechial rash, and headache two weeks after the first AZV dose [31]. Work-up revealed thrombocytopenia (14×10^9/L), VITT, extensive VST, and SAB [31]. He made a complete recovery after urgent thrombectomy, heparin, steroids, and IVIGs, and was discharged with dabigatran for 6 months [31]. VITT-associated SAB was also reported in one of 23 patients with VITT following an AZV dose [32]. In a 54-year-old female disseminated intravasal coagulation with multi-district thrombosis developed 12 days after vaccination with the AZV [33]. A brain computed tomography scan showed multiple subacute intra-axial hemorrhages in atypical locations, including the right frontal and temporal lobes with ipsilateral SAB [33]. Magnetic resonance angiography (MRA) and magnetic resonance venography revealed acute basilar artery thrombosis together with superior sagittal sinus thrombosis [33]. The patient died 5 days later despite maximum therapy. SAB adjacent to the falx was reported in a 22-year-old female 4 days after the first AZV dose [34]. SAB was attributed to VST from VITT [34]. SAB after VITT-associated VST was also reported in a Norwegian healthcare worker in her thirties who experienced fatal ICH with breakthrough to the subarachnoid space one week after the first AZV dose [35].

Vasculitis

Vasculitis is an autoimmune disease affecting the small, medium-sized, or large arteries. Vasculitis is subdivided into several subtypes, one of which is GCA. GCA affects the medium-sized or large arteries, particularly those of the head, especially those of the temples, which is why GCA is also called temporal arteritis. GCA frequently causes headaches, scalp tenderness, jaw pain, or visual impairment. Untreated, it can lead to blindness due to ischemic optic neuropathy. SC2V-related GCA of cerebral arteries has been reported in several patients [3,36]. An 82-year-old male presented with a 4-month history of headaches, jaw claudication, weight loss, bilateral temporo-parietal skin necrosis, and almost complete vision loss, which had developed about 10 days after the second BPV dose [36]. Biopsy of temporal arteries confirmed bilateral, late-stage GCA [36]. In a study of 232,603 vaccinees, vaccination was complicated by GCA in one [3]. In a prospective case study with a median follow-up of 387 days, GCA was reported in a single patient, which worsened during 12 months of follow-up despite immunosuppressive treatment [4]. In a monocentric study of 27 patients with previous immune-mediated disease, SC2V-related GCA was associated with polymyalgia rheumatic [37]. Flares of GCA after SC2Vs have not been reported in a study of 17 GCA patients [38].

Arteritic, anterior, ischemic optic neuropathy (AAION)

is a vasculitis of the small arteritis of the optic nerve. A 79-year-old female developed sudden, bilateral visual loss 2 days after the second BPV dose [39]. At presentation her best-corrected visual acuity was 20/1,250 and 20/40 in the right and left eye on the Snellen acuity chart, respectively [39]. There was pallor of the optic nerve head bilaterally [39]. Temporal artery biopsy was compatible with AAION [39]. She received prednisone with a slow taper and subcutaneous tocilizumab 125 mg weekly [39]. Systemic vasculitis, including the temporal arteries was also reported in an 80-year-old male 7 days after the second dose of an mRNA-based anti-SARS-CoV-2 vaccine [40].

Pituitary apoplexy

Pituitary apoplexy is a rare complication of SC2Vs. Pituitary apoplexy manifests with headache and bitemporal hemianopia. The pathophysiology is explained by bleeding in a pre-existing pituitary adenoma. The bleeding enlarges the tumour and damages not only the pituitary gland but also blocks blood supply to the pituitary gland. The larger the tumor, the higher the risk of a future pituitary apoplexy. A 28-year-old female developed new tension-type headache for one month after the first dose of the Vaxzevira vaccine [41]. After the second dose headache came back, but more intense than after the first dose and in association with amenorrhoea and hyperprolactinemia [41]. Serial MRIs revealed pituitary apoplexy that partially resolved after three months [41]. Pituitary apoplexy was also reported in a 50-year-old male who developed nausea, vomiting, diplopia, and headache 1 day after the third MOV dose [42]. The patient profited from trans-sphenoidal resection [42]. Immune-histochemical evidence for SARS-CoV-2 proteins next to pituitary capillaries was provided [42]. Bleeding was explained by endothelialitis of pituitary capillaries, cross-reactivity of SARS-CoV-2 with pituitary proteins, by coagulopathy due to PF-4 antibodies, or acutely increased blood demand [42]. Pituitary apoplexy 1 day after the second AZV dose was also reported in a 24-year-old female, who manifested with new, sudden-onset frontal headache that benefited from hormone substitution for pituitary insufficiency [43].

Reversible, cerebral vasoconstriction syndrome

RCVS represents a group of conditions that are pathophysiologically characterised by reversible, multifocal narrowing of cerebral arteries with clinical manifestations typically including thunderclap headache and sometimes neurologic deficits due to cerebral edema, ischemic stroke, or seizure. The outcome is usually fair, although major strokes can result in severe disability or death in some patients. SC2V-related RCVS has been first described in a 38-year-old female who developed sudden-onset thunderclap headache together with bilateral scotomas 18 days after the second MOV dose [16]. MRI revealed acute cortical stroke in the territory of the right posterior cerebral artery (PCA) and absence of the PCA on MRA (Fig. 1). Epileptiform discharges were recorded on electroencephalography [16]. The patient benefited significantly from nimodipine and anti-seizure drugs [16]. SC2V-related RCVS has been also reported in a 30-year-old male with a history of RCVS [44]. He experienced an accumulation of RCVS attacks 12 hours after receiving the first BPV dose [44]. The patient profited from losartan, which was given until 3 days after the second dose [44]. The authors concluded that targeting the angiotensin-2-receptor could be a therapeutic and preventive option in patients susceptible for RCVS [44].

Susac syndrome

Susac syndrome is clinically characterised by the trias encephalopathy (encephalitis), occlusion of retinal arteries, and hearing loss. Susac syndrome is due to endotheliopathy mediated through release of perforin and granzym-B from activated cytotoxic CD8 T-lymphocytes. Perforin and granzym-B destroy the blood brain barrier through destruction of endothelial cells. A 50-year-old female developed fever, myalgia, and unilateral scotoma, one month after receiving the Sinovac vaccine (Table 1) [45]. Ophthalmologic investigation revealed paracentral, acute middle maculopathy and neurological work-up aseptic pleocytosis. She was diagnosed with Susac syndrome and profited from empirical antibiotic and virostatic treatment and from high-dose prednisolone [45].

Inflammatory disease

Because SC2V does not primarily induce infection, inflammatory disease following SC2Vs is predominantly immunogenic. Either new onset immunological disease or flares of previously diagnosed immunological disease (e.g., myasthenia, myositis, multiple sclerosis) have been reported as complications of SC2Vs [3].

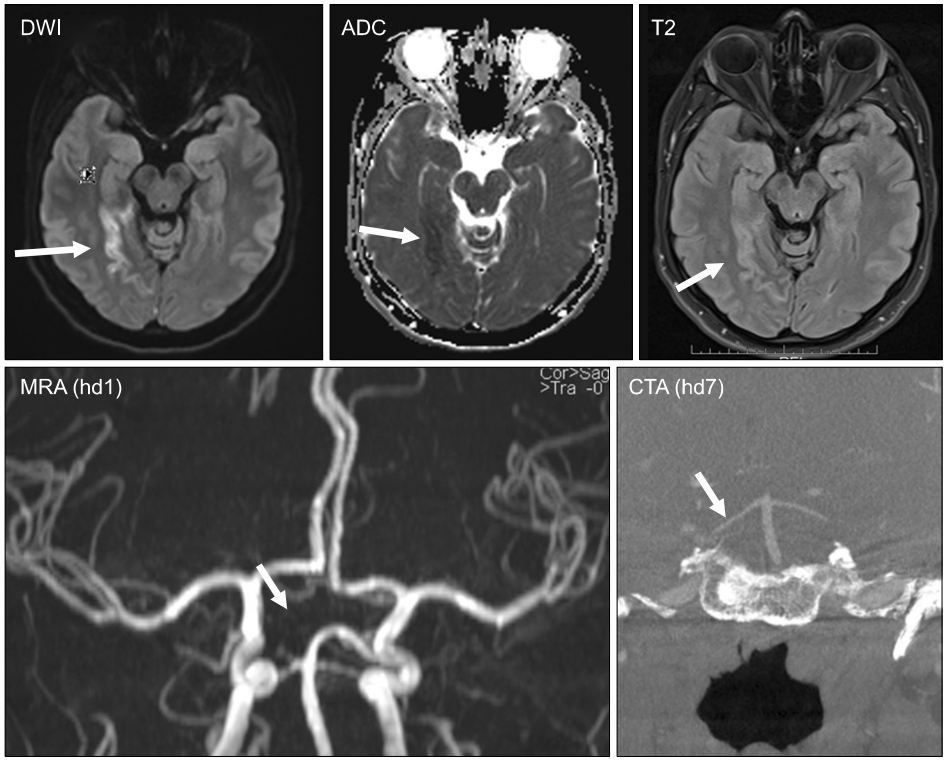

Fig. 1. MRI showing a subacute ischemic stroke in the territory of the right PCA (upper panels) in a 38-year-old female 18 days after the second Moderna vaccine dose. MRA on admission shows discontinuation if the right P1 segment (lower left panel). Normal flow in both PCAs was documented on CTA after 7 days of nimodipine.
MRI, magnetic resonance imaging; MRA, magnetic resonance angiograph; PCA, posterior cerebral artery; CTA, computed tomography angiography; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.
Adapted from the article of Finsterer (Cureus 2021;13:e19987) [16].

Encephalitis

Encephalitis complicating SC2Vs has been repeatedly reported and is usually due the immunological reaction to the vaccine (AIE). In rare cases, encephalitis may be due to superinfection with an infectious agent due to immunosuppression from the vaccination. SC2V-related AIE can be associated with or without specific AIE antibodies (seropositive, seronegative). Various subtypes of SC2V-related AIE have been published, such as non-specific encephalitis with or without AEI antibodies, limbic encephalitis, rhombencephalitis, acute, (hemorrhagic) necrotizing encephalopathy (ANE, AHNE), acute, disseminated encephalomyelitis (ADEM), acute, hemorrhagic encephalomyelitis (AHEM), multifocal necrotising encephalitis (MNE), and cerebellitis.

Non-specific encephalitis: The first reported patient with SC2V-related AIE was a 35-year-old female who developed fever, skin rash, and headache two days after the second BPV dose followed by behavioural changes, and refractory status epilepticus [46]. She was diagnosed with seronegative AIE and recovered upon methyl-prednisolone and plasma exchange [46]. Since then SC2V-related AIE has been reported in several other patients [47-53].

SC2V-related encephalitis with positivity for AIE antibodies has been only rarely reported. A 48-year-old man presented with severe fatigue a few days following his second BPV dose which rapidly evolved in progressive cognitive decline and hyponatremia but recovered under high-dose methyl-prednisolone [54]. He was later diagnosed with anti-leucine rich glioma inactivated-1 (LGI1) positive AIE [54]. Anti-LGI1 AIE is characterized by cognitive impairment or rapid progressive dementia, psychiatric disorders, facio-brachial dystonic seizures and refractory hyponatremia [54]. There is also one report about a female in her twenties who developed N-methyl-D-aspartate receptor positive encephalitis 7 days after the first BPV dose [55].

Limbic encephalitis: Limbic encephalitis after SC2V has been reported in only a few cases. In a case series of 21 patients with neurological autoimmune disease following a SC2V, 1 patient had limbic encephalitis [3]. Limbic encephalitis was also reported in a single patient out of 20 cases with neuro-immunological complications after SC2V and a long-term follow [4]. In a 35-year-old female with seizures two days after the second MOV dose, limbic encephalitis was diagnosed and successfully treated with steroids, IVIG, and rituximab [56]. A case of limbic encephalitis has been also described by Maramotam

in a case series from India [48].

Rhombencephalitis: Rhombencephalitis after a SC2V was reported in a single patient so far [57]. The 30-year-old male, a neurologist himself, reported generalised malaise, headache, hypogeusia, ataxia, and tongue weakness a few weeks after the second BPV dose [57]. He was diagnosed with BPV-associated rhombencephalitis upon imaging and cerebrospinal fluid pleocytosis [57]. He improved significantly upon methyl-prednisolone [57].

Acute, (hemorrhagic), necrotizing encephalopathy: ANE was reported in a 29-year-old female presenting with fever, tachycardia, seizure, and stupor 8 days after vaccination with the BBIBP32-CorV vaccine [58]. MRI revealed bilaterally symmetric hyperintensities in the thalamus and cerebellum, typical for ANE [58]. Serum interleukin-6 was markedly elevated and she carried a *RANBP2* variant, which is typical for familial ANE. The course was complicated by pyelonephritis, acute kidney failure, acute hepatic failure, and septic shock, coma, and death 6 days after presentation [58]. Because the patient was also positive for SARS-CoV-2, it cannot be ruled out that ANE was due to the infection. ANE was also described in a 56-year-old male who presented with fever and akinetic mutism 2 days after the first AZV dose [59]. ANE was diagnosed upon typical, diffusion-weighted imaging hyperintense thalamic lesions on MRI [59]. He also carried a *RANBP2* variant and profited significantly from methyl-prednisolone [59]. AHNE has been reported in a 75-year-old female after the first AZV dose [60]. Despite administration of methyl-prednisolone and IVIGs, the patient died one month after onset [60].

Acute disseminated encephalomyelitis: ADEM is a monophasic autoimmune demyelinating disease of the CNS that typically presents with multifocal neurological deficits and is commonly triggered by viral infections or immunization in genetically susceptible individuals. ADEM occurs more commonly in children than adults. ADEM is diagnosed upon clinical and radiological features. Cerebral imaging shows deep and subcortical white-matter lesions and grey matter lesions in the thalami or basal ganglia. ADEM favourably responds to methyl-prednisolone or IVIGs. There is increasing evidence that SC2Vs of any brand trigger the development of ADEM. It has been reported in several patients meanwhile [48,61-73].

Acute, hemorrhagic encephalomyelitis: AHEM is a rare hyper-acute form of ADEM [74]. AHEM is characterized by fulminant inflammation and demyelination in the brain and spinal cord and is often preceded by an infection or vaccination [74]. SC2V-related AHEM has been reported in a 53-year-old male with rheumatoid arthritis under methotrexate and etanercept who developed fatal AHEM following the second BPV dose [74]. AHEM has been also reported in a case series of three patients after the first AZV dose [75]. Patient-1, a 61-year-old male, and patient-2, a 25-year-old female, benefited from methyl-prednisolone and plasma exchange [75]. Patient-3 died despite application of methyl-prednisolone [75].

Multifocal, necrotizing encephalitis: MNE has been described in a single patient so far. A 76-year-old male with Parkinson's disease (PD) experienced pronounced cardiovascular side effects, which were not specified, after the first AZV dose [76]. After the second BPV dose, behavioural and psychological changes were noticed [76]. He did not want to be touched anymore and presented with increased anxiety, lethargy, and social withdrawal even from close family members [76]. Additionally, striking worsening of PD was noted, leading to severe motor impairment and recurrent need for wheelchair support [76]. Two weeks after the third vaccination with the BPV, he suddenly collapsed but recovered [76]. One week later, he collapsed again due to cardio-pulmonary arrest but was successfully resuscitated after $>$ 1 hour [76]. Unfortunately, he died shortly after starting mechanical ventilation. Autopsy and histopathological analyses of the brain uncovered acute, predominantly lymphocytic vasculitis and MNE with pronounced inflammation including glial and lymphocytic reaction [76]. In the heart, signs of chronic cardiomyopathy as well as mild acute lympho-histiocytic myocarditis and vasculitis were found [76]. Because only the spike protein (S-protein) but no nucleo-capsid protein could be detected within the foci of inflammation particularly in the endothelial cells of small blood vessels, of both, brain and heart, the condition was attributed to the vaccination rather than to a SARS-CoV-2 infection [76].

Cerebellitis: Cerebellitis has been only rarely reported as a complication of SC2Vs. In a 39-year-old female with stable multiple sclerosis since age 22 under treatment with interferon, natalizumab, and ocrelizumab, developed fatigue, fever, and sopor 17 days after the first BPV dose [77]. Cerebellitis was diagnosed that required posterior fossa decompression for imminent herniation [77].

She died six months after onset following deterioration of multiple sclerosis and development of tetraplegia, bulbar involvement, and recurrent pulmonary infections after having been switched to cladribine [77].

Meningitis

Only few cases with SC2V-related aseptic or infectious meningitis have been reported. In a multicentre study on the reactivity to the AZV vaccine in 4,478 healthcare workers, vaccination was complicated by aseptic meningitis in only a single patient [5]. In two other patients, a 43-year-old female and a 38-year-old female, aseptic meningitis developed 4 and 10 days after the second and first dose of the BPV respectively [78]. Both patients presented with fever, headache, neck pain, and generalised papulous exanthema, lymphocytic pleocytosis, but both recovered completely upon symptomatic treatment [78]. A 42-year-old female developed aseptic meningitis seven days after the first BPV dose but also recovered completely [79]. Aseptic meningitis was also reported in a 17-year-old female who developed fever and severe headache, three weeks after the first BPV dose [80]. Work-up revealed optic disc edema, multifocal well-circumscribed chorio-retinal lesions in the periphery, and aseptic pleocytosis [80]. Multiple evanescent white dots syndrome was diagnosed [80]. Clinical manifestations and abnormal findings resolved spontaneously within one month [80]. Several other cases have been reported.

Demyelinating disorders

There are a number of reports about vaccinees which reported newly onset or flares (exacerbations) of demyelinating CNS disorders following a SC2V [81]. Newly onset or exacerbating demyelinating disorders reported after SC2Vs include multiple sclerosis [81,82], cerebral isolated syndrome [81], optic neuritis [83], neuromyelitis optica (NMO) spectrum disorders (NMOSD) [84-86], and myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOGAD) [62]. There is also one report about a 56-year-old female who developed a tumefactive, demyelinating, subcortical lesion 2 days after the first AZV dose [87]. A number of patients with encephalomyelitis and MOG antibodies following SC2V have been reported [83]. One of these patients presented with optic neuritis 10 days after a booster with the BPV [83]. Complete recovery was achieved with high-dose steroids [83]. At least 20 other cases have been reported [83].

Transverse myelitis

Generally, SC2V-related transverse myelitis can occur together with optic neuritis or encephalitis, with both, or can occur as an isolated condition. Isolated transverse myelitis manifests with motor, sensory, and autonomic deficits, and has been repeatedly reported as a complication of SC2Vs. In a meta-analysis of 49 studies, transverse myelitis was reported in 20 cases [61]. In a prospective study of 25 patients with SC2V-related acute inflammatory CNS disease, transverse myelitis was found in 4 [62]. Patients with SC2V-related transverse myelitis are frequently positive for MOG-IgG [62]. In a study of 476 children with mulitsystem inflammatory syndrome in children (MIS-C) and neurological deficits, one child had transverse myelitis [88]. A rare subtype of transverse myelitis, known as longitudinally extensive transverse myelitis extending over $>$ 3 cord segments, has been reported as a complication of SC2Vs in some patients [89-92]. The most common therapy of SC2V-related transverse myelitis is methyl-prednisolone.

Epilepsy

Newly onset seizures are a common complication of SC2Vs. SC2V-related seizures may be due to other CNS disease occurring as a complication of SC2Vs or may occur in the absence of another CNS disease. Seizures may go along with or without structural lesions on cerebral imaging. Symptomatic epilepsy may be due to ischemic stroke, bleeding, VST, encephalitis, meningitis, or other CNS disorders manifesting with structural lesions. If vaccinees develop seizures after SC2V in the absence of a structural lesion, they should undergo CSF investigations to rule out encephalitis/meningitis. In patients with a history of epilepsy there is no increase in seizure frequency or severity. Some patients developed status epilepticus after a SC2V. In a single patient status epilepticus was attributed to systemic capillary leak syndrome (SCLS) [93]. SCLS is a rare but potentially life-threatening disorder clinically manifesting with recurrent episodes of arterial hypotension, hypalbuminemia, elevated haematocrit, and generalised edema. SCLS is due to endothelial hyper-permeability triggered by viral infections or vaccinations. SCVS is increasingly recognised as a complication of SC2Vs but has been only rarely described to manifest with neuro-

logical compromise. A 36-year-old male was admitted for syncope, hypotension, and tachycardia and developed status epilepticus, cardiac arrest, anasarca, acute kidney injury, disseminated intravascular coagulation, pulmonary edema, rhabdomyolysis, and pleural effusions on hospital day 3 [93]. He was diagnosed with SCLS and recovered completely [93].

Other SC2V-related CNS complications

Several other CNS complications of SC2Vs have been occasionally reported (Table 2). These include opsoclonus myoclonus syndrome (OMS), narcolepsy, Tolosa Hunt syndrome, cytotoxic lesions of the corpus callosum, neuroleptic malignant syndrome, hypophysitis, the wine glass sign, idiopathic intracranial hypertension, and isolated adeno-corticotropic hormone deficiency (Table 2). Although OMS has been repeatedly reported as a complication of COVID-19 in pediatric and adult patients, it was only rarely reported as a complication of a SC2V [48]. In an Indian study, a single patient with OMS after SC2V has been reported [48]. The patient was a 65-year-old male who developed behavioural changes 10 days after the second AZV dose [48]. Over the next three weeks jerky movements became apparent. There was mild pleocytosis. OMS was diagnosed and he profited from IVIGs and methyl-prednisolone [48]. Narcolepsy is due disturbed sleep-wake cycle regulation and characterised by excessive daytime sleepiness and brief involuntary sleep episodes. Narcolepsy can be associated with cataplexy (sudden loss of muscle strength) in 70% of cases or without. It may go along with or without structural cerebral lesions in the hypothalamus or brainstem. Narcolepsy with cataplexy is evidenced to be an autoimmune disorder. The first reported patient with SC2V-related narcolepsy was a 57-year-old female, who developed narcolepsy and impaired memory immediately after the first BPV dose [94]. Despite this reaction she received the second dose and experienced the same side effects but this time more intense than before [94]. The patient did not carry human leukocyte antigen alleles associated with narcolepsy [94]. There are also case reports documenting aggravation or exacerbation of Kleine Levin syndrome, hypersomnia, excessive daytime sleepiness, and narcolepsy after SC2V [95].

CNS disease due to vaccination-related complications outside the nervous system

CNS disease after a SC2V may not only be due to primary but also secondary affection of the CNS. Secondary CNS complications of SARS-CoV-2 vaccines mainly include embolism to the brain due to endocarditis, myocarditis, intraventricular thrombus formation, heart failure, or arrhythmias. Physicians should be aware of cardiac complications after SC2Vs and should consider a cardiogenic origin of cerebrovascular disease after a SC2V. There are also reports about patients who experienced breakthrough infections of the CNS after SC2Vs. For example, infectious meningitis due to reactivation of the zoster virus was reported in a 12-year-old male 11 days after the first BPV dose [96]. The patient recovered completely upon intravenous acyclovir [96]. VIIT and SCLS are also well-known for causing secondary CNS disease.

PNS Adverse Reactions

Side effects of SC2Vs concerning the PNS include cranial nerve lesions (hypogeusia, ageusia hyposmia, anosmia, trigeminal neuralgia, facial palsy, abducens palsy), spinal nerve lesions (Parsonage Turner syndrome [PTS], small fiber neuropathy [SFN]), both (Guillain Barre syndrome [GBS], myasthenia), or the skeletal muscles (myositis/dermatomyositis, rhabdomyolysis) (Table 3). The most common SC2V-related PNS complications are cranial nerve lesions, GBS, and myositis.

Cranial nerve lesions

The cranial nerve most commonly affected from SC2Vs is the facial nerve (cranial nerve VII). Only in some patients affection of other cranial nerves (I, V, VI, VIII, IX) has been reported. Whether facial palsy is due to the same pathophysiological mechanism as viral infection-related facial palsy is under debate. Because facial palsy is also a common manifestation of GBS it is also conceivable that isolated facial palsy represents an abortive form of GBS. Hypogeusia, ageusia hyposmia, and anosmia have been also reported as complications of SC2Vs but are less common than in SARS-CoV-2 infections. In a prospective, exploratory observational study on 258 vaccinees having received either AZD1222 or BBV152, only 0.8% reported ageusia [97]. SC2V-related trigeminal neuralgia has been only reported in three patients [98,99]. The first patient is a 77-year-old female with a history of microvascular de-

Table 3. Mild, moderate, and severe side effects of SARS-CoV-2 vaccinations affecting the PNS

PNS side effects	Frequency	Reference
Cranial nerve affection		
Facial palsy	+++	[108]
Abducens palsy	+	[119]
Oculomotor palsy	+	[120]
Ageusia, anosmia	+	[20]
Multiple cranial nerve palsy	+	[121]
Trigeminal neuralgia	+	[99]
GBS and subtypes	+++	[101]
Parsonage Turner syndrome	++	[104]
Small fibre neuropathy	++	[122]
CIDP	+	[103]
Cubital tunnel syndrome	+	[123]
Flares/new onset myasthenia gravis	+	[124,125]
Myositis, myalgia	+++	[4,126]
Dermatomyositis	+	[106]
Rhabdomyolysis	+	[127]
IgG-related orbital myopathy	+	[128]
Multifocal motor neuropathy	+	[129]

+, rare; ++, repeatedly reported; +++, common; PNS, peripheral nervous system; GBS, Guillain Barre syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy.

compression for previous trigeminal neuralgia [99]. One month later, she received the first BPV dose [99]. Twelve hours after vaccination she experienced pain and numbness in the face. Antibodies against the zoster virus were negative. Carbamazepine and pregabalin improved the condition but right-sided facial numbness persisted [99]. The second patient is a 45-year-old female who developed trigeminal neuralgia 3 days after having received the first BPV dose [98]. Because NSAR did not result in complete discontinuation of the complaints, pregabalin was started [98]. However, also pregabalin did not result in complete recovery, why glucocorticoids were given with success [98]. The third patient is a 48-year-old male who complained of left-sided facial pain (stabbing, electric shock-like) one day following the second BPN dose [100]. After one week, additionally numbness of the left upper limb developed. He received steroids, which were tapered and resulted in almost complete recovery at the three-months follow-up [100].

Guillain Barre syndrome

GBS is a neuro-immunological disorder due to an autoimmune reaction against components of the PNS affecting the roots of cranial or peripheral nerves. Depending on the site of the antibody attack (myelin sheath or node of Ranvier), demyelinating and axonal forms are delineated. The most common subtypes of GBS are acute, inflammatory, demyelinating polyneuropathy (AIDP), acute, motor, axonal neuropathy (AMAN), acute, motor and sensory, axonal neuropathy (AMSAN), Miller–Fisher syndrome, pharyngo-cervico-brachial variant, mono- or polyneuritis cranialis, and Bickerstaff encephalitis. In the Western world the most common subtype is AIDP whereas in Asia AMAN, and AMSAN prevail. Clinical presentation and treatment of SC2V-related GBS is not at variance from GBS due to other causes. More than 300 cases of SC2V-related GBS have been reported to date [3,4, 101]. Prevalence of SC2V-related GBS varies considerably between studies. In a study of 2,163 GBS patients, vaccination with the AZV was associated with an increased risk of GBS [102]. In a prospective case study with a median follow-up of 387 days, GBS developing within 6 weeks after SC2V in only four patients [4]. Although there is an ongoing debate whether GBS is truly causally related to SC2Vs, more arguments speak for than against a casual relation.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

CIDP is characterised by symmetric sensorimotor deficits in the limbs and diagnosed according to European Federation of Neurological Sciences criteria. In an ambispective, multicentre hospital-based cohort study carried out between March to October 2021 in India on the neurological side effects of anti-SC2Vs with the AZV or BBV152 (Covaxin), a single patient developed CIDP [103].

Plexitis (Parsonage Turner syndrome)

PTS is clinically characterised by neuralgic neck and shoulder pain, muscle weakness, and sensory disturbances. Only few cases with SC2V-related PTS have been reported [104]. Patients with SC2V-related PTS usually recover partially under steroids, analgesics, and occupational therapy, but complete recovery can take months.

Small fiber neuropathy

SFN is due to affection of A-delta fiber or C-fibers and manifests clinically with pain in a highly variable distribution, sensory disturbances, and autonomic dysfunction. The golden standard for diagnosing SFN is skin biopsy showing reduced intra-epidermal nerve fiber density or

reduced sweat gland nerve fiber density. Nerve conduction studies are usually normal unless SFN is associated with large-fiber neuropathy. SC2V-related SFN has been first described in a 57-year-old female who presented with burning dysesthesia initially in the feet and consecutively spreading to the calves, and minimally to the hands one week after the second BPV dose [105]. Several other biopsy-proven cases have been reported since then.

Myasthenia

Several patients with newly onset myasthenia or exacerbation of myasthenia after SC2V have been reported. In a prospective case study with a median follow-up of 387 days, myasthenia was reported in a single patient [4]. In a study of > 200,000 vaccinees, one patient developed myasthenia [3]. In a multi-centre study from India, only one developed myasthenia [103]. Treatment of SC2V-related myasthenia is not at variance from myasthenia due to other causes.

Myositis or dermatomyositis

Myositis is a common complication of SC2Vs [3,4] but often remains a suspicion due to unavailability of muscle MRI or muscle biopsy [103]. Because myalgia is a common complication of SC2Vs, and because these patients often present with creatine-kinase (CK) elevation, myositis is suspected. Myositis-specific antibodies are usually absent in these patients. A few patients have been reported who developed dermatomyositis after a SC2V [106].

Rhabdomyolysis

Rhabdomyolysis is due to acute muscle cell necrosis and manifests clinically with fatigue, myalgia, exercise intolerance, cola-coloured urine, or even muscle weakness. Causes of rhabdomyolysis are variegated but in association with SC2V it may be due to myositis, previous seizure, or SCLS. A 38-year-old Brazilian male was admitted for intense pain in lower limbs, rock hard calves, arthro-myalgia, diarrhea, and some isolated episodes of fever [107]. One day prior to onset of symptoms he had received the second BPV dose [107]. On admission, there was arterial hypotension, hypoalbuminemia, the haematocrit was 70%, lactic acidosis (6.88 mmol/L), and renal insufficiency [107]. On hospital day 2 he developed rhabdomyolysis with a CK value of 39,000 U/L and respiratory failure and required mechanical ventilation. After ruling out all differential diagnoses, SCLS was diagnosed and rhabdomyolysis attributed to increased compartment pressure [107]. The patient recovered completely upon symptomatic treatment [107]. A 68-year-old female was admitted for nausea/vomiting, syncope, hypotension, and tachycardia [93]. Consecutively, she developed protracted hypotensive shock, anasarca, acute kidney failure, disseminated intravascular coagulation, bilateral lower-extremity compartment syndrome with rhabdomyolysis, and widespread digital necrosis [93]. She was diagnosed with SCLS but deceased despite maximum treatment [93].

VACCINES UNDER DEVELOPMENT OR UNDER APPROVAL

In addition to approved and marketed anti-SARS-CoV-2 vaccines a number of vaccines are in development or approval. In a randomised, placebo controlled phase 1/2 trial, the recombinant protein-based anti-SARS-CoV-2 vaccine S-268019 (Shionogi, Japan) was rated as safe in adults up to day 50. The vaccine elicited a robust IgG antibody response, but failed to elicit adequate levels of neutralising antibodies. In a randomised, observer-blinded, phase 2/3 study, S-268019-b demonstrated non-inferiority to BNT162b2 on the co-primary endpoints for neutralizing antibodies. Most participants reported mild reactogenicity on days 1−2, the most common being fatigue, fever, myalgia, and injection-site pain but no serious adverse events. In a study of the protein-based SARS-CoV-2 vaccine MVC-CPV1901 (Dynavax, Taiwan) on healthy adolescents, the most commonly reported adverse events were pain, tenderness, malaise, and fatigue. No serious adverse events were reported. In another study on the effect of booster doses of the MVC-CPV1901 vaccine mild or moderate adverse events were reported. In a cohort study on the efficacy and tolerability of the CIGB-66 (Abdala) vaccine (CIGB, Cuba), no serious adverse events were reported in any of the enrolled Cuban vaccinees. In a study of 480 participants who received the third booster dose of the ZF2001 (Zifivax) vaccine (Anhui Zhifei Longcom, China), the incidence of adverse reactions within 30 days of vaccination was 5.8%. No serious adverse events were reported in this study either. Numerous other anti-SARS-CoV-2 vaccines are being studied (e.g., ARCT-154, Noora-vaccine, Turcovac, SCTV01C, COVID-19 vaccine Hipra, DelNS1-2019-nCoV-RBD-OPT1, Covax19, Razi Cov-Pars,

CoviVac, GRAdCOV2, VXA-CoV2-1, ChulaCoV19, BBV154, PTX-COVID19-B, SC-Ad6-1, ReCOV, ABNCoV2, GX-19N, EpiVacCorona, AV-COVID-19, rVSV-SARS-CoV-2-S, BECOV2, GBPS10, COVAC-1DS-5670a etc.) but most have either had no serious adverse reactions reported or the profile of side effects has not yet been evaluated in clinical trials.

DISCUSSION

This review shows that the spectrum of neurological side effects of SC2Vs is broad, ranging in severity from mild to severe, and that the outcome ranges from full recovery to death. Most of these neurological side effects are due to the physiological or an enhanced immune response to the vaccine or its components. However, the immunological response to the vaccine can also be diverse. Several explanations have been proposed to clarify the pathophysiology of the neurological side effects of SARS-CoV-2 vaccines. According to one of them, adverse reactions result from vaccine-induced S-protein generation. According to this hypothesis, the S-protein or some of its peptide fragments not only stimulate the immune system, but also bind to angiotensin converting enzyme-2 (ACE-2) receptors not only on endothelial cells but also on several cell types surrounding the capillary beds. Through this mechanism, S-protein enters the cell and stimulates a series of intracellular reactions, mimicking SARS-CoV-2 infection. There is also evidence that adverse reactions result from the abundance of ACE2 receptors on cell surfaces. When ACE2 receptors are upregulated, which is the case with nicotine or anti-cancer drugs, SARS-CoV-2 infections can be more severe. When ACE2 upregulation is suppressed by inhibition of transient receptor potential canonical (TRPC3)-NADP oxidase (Nox2) complex formation, pseudovirus-induced contractile and metabolic dysfunction of rat myocardiocytes can be attenuated. These results suggest that downregulation of ACE2 expression could represent a future therapeutic option of SARS-CoV-2. A third hypothesis suggests that adverse reactions result from the induction of a pro-inflammatory response by nano-particles used for mRNA delivery (pegylation). There is also some evidence that SARS-CoV-2 vaccines elicit an allergenic response, reflected in reports about vaccination-induced mast cell activation syndrome. Arguments supporting this hypothesis are skin lesions and the beneficial effect of antihistamines in some patients after SC2Vs. This hypothesis is further supported by two reports of chronic, spontaneous urticaria (CSU) after SC2Vs. The likelihood of CSU recurrence within three months of BPV was correlated with a positive autologous serum skin test, allergic comorbidities, and basopenia. Some authors also propose that all adverse reactions of SARS-CoV-2 vaccines can be explained by MIS-C/MIS-A. An argument for MIS-C/MIS-A is that inflammatory markers, such as cytokines, chemokines, glial factors, 14-3-3, and others are often found elevated in patients with SARS-CoV-2 vaccine side effects. Another hypothesis suggests that SARS-CoV-2 vaccines cause side effects by suppressing the immune response via G-quadruplexes, exosomes, and microRNAs. One argument for this is that SC2Vs can reduce immune competence and can cause superinfections or flares of pre-existing immunological disease or even trigger a new immunologic disease. The role of VITT should not be neglected in terms of side effect generation, but VITT does not occur in every vaccinee who develops side effects. There are also side effects that cannot easily be explained by thrombosis of venoles, arterioles, or larger vessels. It is also speculated that SCLS may play a role in the pathophysiology of neurological side effects. However, not all patients with SARS-CoV-2 vaccine side effects develop SCLS, so it cannot be used as a general explanation for SC2V-related side effects.

CONCLUSIONS

Neurological adverse reactions occur with any type of SARS-CoV-2 vaccine, are varied, can range from mild to severe, treatable or hardly treatable, and should be taken seriously to initiate early treatment and thus improve the outcome and avoid fatalities.

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