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Spike-Induced Disturbances (SPAS*): An Analysis of Common Suspected Adverse Experiences Associated With Covid-19 Vaccines

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Abstract

This review/analysis gives a first impression of numerous adverse events related to Covid-19 vaccination, which have received little attention to date, are often unexplained, but are nevertheless very distressing. Frequently observed organ-related ADRs after Covid-19 vaccination were such of the nervous system, musculoskeletal system, gastrointestinal tract, and skin.

The involvement of almost all organs in the side effect spectrum of Covid-19 vaccines demonstrates their systemic efficacy. As shown by the ADRs occurrence even after numerous days to weeks, the duration of spike production obviously lasts longer than claimed.

The key role is played by the interaction between the spike subunit S1 and the membrane-bound enzyme ACE2, the receptor for SARS-CoV. Downregulation of ACE2 by spikes and following activation of RAAS can lead to numerous clinically relevant disorders, such as vasoconstriction, tissue ischemia, induction of proliferative processes, increased oxidative stress, inflammation, or coagulation disorders, as previously shown for cardiovascular reactions. It is proposed to use the collective term "SPAS" (in German: Spike ausgelöste Störungen) - spike induced disturbances for side effects based on this mode of action.

The common mode of action and only slightly different frequencies of adverse events and fatal outcomes do not indicate any principal differences in adverse event profiles of the individual spike-based Covid-19 vaccines. A class-specific side effect profile can be assumed.

Knowledge and awareness of the comprehensive adverse event profile of the novel Covid-19 vaccines and their potential dangerousness may improve vaccine safety.

Keywords: Adverse reactions; cardiovascular system; class specific action; common mode of action; gastrointestinal system; musculoskeletal system; nervous system; skin; spike/ACE2-interaction; spike-based Covid-19 vaccination.

Abbreviations

*SPAS is the abbreviation of "Spike ausgelöste Störungen" (in German).

Introduction

SARS-CoV-2 coronavirus has affected the health of the world's population over the past two years, triggering numerous harmful and incomparably profound socio-economic consequences. The virus not only affects the respiratory tract, but also has numerous extra-pulmonary manifestations (Gupta et al., 2020); (Zheng et al., 2020). Thus, in addition to direct viral cytotoxicity and acute anaphylactic/allergic, immunologic, and known respiratory effects, several cardiovascular, gastrointestinal, renal, metabolic, endocrine, reproductive, nervous system, and skin-related dysfunctions and impairments have been reported to date in association with Covid-19 disease (Gupta et al., 2020). For example, 20-30% of patients hospitalized with Covid-19 suffered myocardial injury, 17% suffered cardiac arrhythmias including heart block, 12-61% of Covid-19 patients experienced gastrointestinal manifestations; neurological symptoms occurred in 36% of patients with severe disease and approximately 44% had cutaneous findings at disease onset (cited by (Gupta et al., 2020)). The reason for the involvement of these organs in the

Covid-19 disease pattern appears to be the presence of the cell entry receptor ACE2, which provides the basis for tissue tropism of SARS-CoV-2.

Since the conditional marketing authorization (CMA) of Covid-19-vaccines in European countries, millions of healthy people have been vaccinated with beneficial effects. Unfortunately, reports of suspected adverse reactions are accumulating, affecting almost all organ systems, especially those also affected by Covid-19 disease (EudraVigilance, n.d.); (Finsterer, 2021). It is reasonable to assume that vaccine spikes, like viral spikes, occupy the receptor enzyme ACE2 in the same mode. However, this enzyme plays a potent counterregulatory role in the RAAS pathway. Its downregulation by SARS-CoV-2 or by isolated spikes may induce RAAS activation, particularly an increase in angiotensin II. Acute pathophysiological consequences and long-term disturbances may occur. The first comprehensive analysis of cardiovascular adverse reactions following vaccination with Comirnaty® and Vaxzevria® vaccines has strengthened the suspicion of an association with this mode of action (Lehmann, 2021). Cardiovascular side effects are among the most dangerous associated with Covid-19 vaccination, but nervous system and musculoskeletal disorders are the most common organ system-related ADRs followed by gastrointestinal, infectious and skin disorders (sources, pl. see (EudraVigilance, n.d.)).

The question arises as to whether there might also be a relationship between these very common adverse experiences and the spike/ACE2 interaction.

First, the current frequencies of the corresponding ADRs were determined. The available spontaneous reports of the EudraVigilance database served as the basis for relevant data. A publicly available German internet portal with comparatively comprehensive individual information was used as an additional data source (Nebenwirkungen der Covid Impfungen. (n.d.)). Relevant published findings and laboratory results from the German Internet portal helped to interpret the results and their possible causation.

Materials and Methods

This review and analysis was not based on clinical trials. It deals with the evaluation of anonymously reported adverse events in vaccinated healthy individuals in publicly available databases or reports. Individual identification was not possible. According to the ethics committee of the Saxon State Medical Association (SLÄK), an ethics vote is not necessary for anonymized, non-personalized data.

Data were retrieved from the Web Reports of EudraVigilance (EudraVigilance, n.d.) of the European Medicines Agency (EMA) and the German internet portal (Nebenwirkungen der Covid Impfungen, n.d.).

EudraVigilance is a system for recording reported suspected adverse reactions. The EudraVigilance system allows the detection of signals of suspected side effects that are previously unknown and of new information on known side effects. Therefore, it seems suitable for answering the questions raised. The EudraVigilance database is updated weekly and the data are constantly growing. The cut-off dates were February 13th , 2022 (all suspected adverse reactions and related fatalities, as well as organ system-related ADRs after vaccination with Tozinameran/Comirnaty®, SpikeVax®/Moderna, Vaxzevria®/ AstraZeneca, and the Janssen vaccine) and February 11th, 2022 (ADRs of the nervous and musculoskeletal systems as well as the skin).

The total number of deaths was evaluated by summing the fatal outcomes in all 27 defined reaction groups (Table 6 of the EudraVigilance System). Number of individual cases for selected reactions resp. search terms were retrieved from the reaction groups in Tab. 6 EudraVigilance System, which provides the most detailed level of information. For quantification, the total number of individual cases and ADRs was used.

The German internet portal "nebenwirkungen-covid-impfung.org" (Nebenwirkungen der Covid Impfungen, n.d.) is a freely accessible forum for sharing experiences with Covid-19 vaccination. It provides a comprehensive and detailed description of the symptoms of affected individuals. In addition, sex, age, weight, vaccine, date of vaccination, batch number of vaccine*, onset of symptoms, course*, treatment attempts*, special examination findings*, previous illnesses, emergency or hospital admissions and reporting of this side effect were documented (*not sufficiently documented in each individual case). On December 22, 2021, I became aware of the collection of 220 individual case representations.

Frequency and percentage were used to quantitatively describe adverse experiences and fatal outcomes.

All information on the included suspected side effects should not be considered or interpreted as meaning that the vaccine causes the observed effect or is unsafe to use.

Results

1. Overview of adverse reactions in association with Covid-19 vaccines through February 13, 2022 (Web reports of EudraVigilance database):

From June 5, 2021 (Lehmann, 2021) to February 13, 2022, the total number of vaccines with adverse events nearly tripled (2.87-fold), as did the number of deaths associated with adverse events (2.88-fold, pl. see Table 1. a). SpikeVax® showed a particularly significant increase in ADRs (to 210%, Tab. 1. a). The increasing trend (cumulative number of vaccinated individuals with adverse events) is unbroken, especially in association with Comirnaty® ((EudraVigilance, n.d.): number of individual cases received over time). A relatively high percentage of side effects ended fatally (side effect lethality: 2.34-4.9%, Table 1. a).

The Vaxzevria® is an exception. From June to July 2021, the trend has flattened significantly, and the monthly reporting

numbers have declined substantially from 100% to 57% (below 20,000/month since October 2021, (EudraVigilance, n.d.) and Table 1. a). It is believed that restrictions on use due to known side effects contributed to this finding.

Vaccine	Individual cases with suspected adverse reaction (n; individual cases/day; change in % since June 5, 2021)	Suspected adverse reactions (n)	Fatal outcomes (n)	Fatal outcomes (% of individual cases with adverse reaction)
Comirnaty®/Tozinameran (since December 8th 2020 in the UK, 432 days)	775 829 1 796/day **152%**	1 791 261	18 185	2.34
SpikeVax®/Moderna (available since approximately January 11th 2021, 398 days)	233 461 587/day **210%**	573 035	11 093	4.75
Vaxzevria®/AstraZeneca (available since approximately February, 1st 2021, 377 days)	450 733 1 196/day **57%**	1 170 321	8 174	1.81
Janssen (since about March 12th 2021, 338 days)	50 953 151/day **151%**	131 394	2 500	4.9
Total	**1 510 976** June 5, 2021*: n= 525 907	**3 666 011**	**39 952** June 5, 2021*: n= 13 867	

*data from (Lehmann, 2021)

Table 1.a: Total individual cases with any suspected adverse reaction, total suspected adverse reactions and fatal outcomes after vaccination up to February 13th, 2022 (EudraVigilance)

Adverse reactions affecting the nervous system (16.2-20.2% of all ADRs) were reported most frequently, followed by those affecting the musculoskeletal (11.7-14.5%) and gastrointestinal systems (7.5-9.3%), as well as the skin (3.0-5.1%; pl. see Table 1.b). Infections and respiratory disorders occurred at a similar frequency (3.5-6.8%). Adverse reactions in the cardiac and vascular disorders reaction groups were less frequent represented (1.8-3.4% respectively 2.2-2.9%).

Surprisingly, almost equal numbers of adverse events ended fatally in the cardiac (8.4-14.5%), infection/respiratory (7.8-13.7%), and nervous system (9.4-14.7%) reaction groups. This suggests a similar severity of adverse events in the reaction groups.

Reaction group (RG)	Comirnaty®/Tozinameran (n; % in relation to all ADRs and to fatal outcomes)	SpikeVax®/Moderna (n; % in rel. to all ADRs and to fatal outc.)	Vaxzevria®/AstraZeneca (n; % in rel. to all ADRs and to fatal outc.)	Janssen (n; % in relation to all ADRs and to fatal outcomes)
Sum of ADRs/- *fatal outcomes* from all 27 RGs	**1 791 261** ***18 185***	**573 035** ***11 093***	**1 170 321** ***8 174***	**131 394** ***2 500***
nervous system disorders	290 349 16.2%	95 946 16.7%	236 745 20.2%	23 989 18.3%
fatal outcome	*1 926 10.6%*	*1 040 9.38%*	*1 199 14.7%*	*248 9.92%*
musculoskeletal and connective tissue disorders	209 669 11.7%	70 107 12.2%	170 055 14.5%	17 493 13.3%
fatal outcome	*228 1.25%*	*221 1.99%*	*171 2.1%*	*57 2.28%*
gastrointestinal disorders	138 253 7.7%	46 468 8.1%	108 425 9.3%	9 791 7.5%
fatal outcome	*706 3.9%*	*416 3.75%*	*447 5.45%*	*94 3.76%*

infections and infestations	84 884	4.7%	24 462	4.3%	43 810	3.7%	8 881	6.8%
fatal outcome	*1 931*	*10.6%*	*1 051*	*9.5%*	*634*	*7.76%*	*211*	*8.44%*
skin and subcutaneous tissue disorders	81 815	4.6%	29 172	5.1%	52 622	4.5%	3 894	3.0%
fatal outcome	*146*	*0.8%*	*96*	*0.87%*	*69*	*0.84%*	*12*	*0.48%*
respiratory, thor. and mediast. disord.	75 926	4.2%	*24 308*	*4.2%*	*42 021*	*3.6%*	*4 649*	*3.5%*
fatal outcome	*1 932*	*10.6%*	*1 178*	*10.62%*	*1 119*	*13.69%*	*314*	*12.56%*
reproductive system and breast disorders	74 588	4.2%	14 047	2.5%	17 181	1.5%	3 189	2.4%
fatal outcome	*6*	*0.03%*	*9*	*0.08%*	*3*	*0.04%*	*7*	*0.28%*
cardiac disorders	61 233	3.4%	19 462	3.4%	21 330	1.8%	2 671	2%
fatal outcome	*2 638*	*14.51%*	*1 169*	*10.5%*	*854*	*10.45%*	*211*	*8.44%*
blood and lymph. system	50 761	2.8%	13 383	2.3%	14 038	1.2%	1 272	0.97%
fatal outcome	*254*	*1.4%*	*120*	*1.08%*	*279*	*3.41%*	*54*	*2.16%*
vascular dis.	44 247	2.5%	12 579	2.2%	29 128	2.5%	3 792	2.9%
fatal outcome	*799*	*4.4%*	*405*	*3.65%*	*542*	*6.63%*	*175*	*7%*

** Reaction groups without relevance and/or with lower incidence were excluded: general disorders and administration site conditions, injury, poisoning and procedural complications, investigations, surgical and medical procedures, ear and eye disorders, immune system disorders, metabolism and endocrine disorders, psychiatric disorders, renal and hepatobiliary disorders, neoplasms, pregnancy and product issues, social circumstances, congenital conditions.*

Table 1. b): The organ systems most frequently affected* (13.2.2022, (EudraVigilance, n.d.))

A few deviations were registered in association with Vaxzevria® and Janssen vaccination (Vaxzevria®: relatively low frequencies in the reaction groups 'reproductive system', 'blood and lymphatic system', and 'cardiac disorders'; Janssen: low rate in the reaction group 'blood and lymphatic system'; high rate in the reaction group 'infections').

Apart from these deviations, it is noteworthy that the percentage frequencies of adverse events and fatal outcomes of the four Covid-19-vaccines in the specific reaction groups were always close to each other. That is, the adverse event profiles of these four vaccines are very similar, if not identical, and thus class-specific to spike-based vaccines.

2. Musculoskeletal and nervous system symptoms (Web reports of EudraVigilance database):

The broad spectrum and frequency of adverse reactions assigned to the reaction groups 'musculoskeletal and connective tissue disorders' and 'nervous system disorders' was surprising. In addition to common complaints such as dizziness, headache, or muscle pain/myalgia, these groups also summarized a number of unusual symptoms not previously associated with conventional vaccinations.

Symptoms were dominated by myalgias (50-64% of ADRs in the reaction group; approximately 14-22% of all individual cases; pl. see Table 2. a), supplemented by cases of musculoskeletal pain. Muscular weakness was reported by 0.8-1% of those affected by side effects, spasm by 0.7-1.2%, and muscle twitching by 0.14-0.21%.

Rare cases included paresis (n=441; 0.03%), rhabdomyolysis (n=407; 0.028%), myoclonus (n=338; 0.02%), muscle atrophy (n=249; 0.017%), and myokymia (n=54; 0.004%).

vaccine	muscle spasms (n;%)	twitching (n;%)	myoclonus (n;%)	myokymia (n;%)	myalgia (n;%)	musculoskeletal pain (n;%)	paresis (n;%)	muscular weakness (n;%)	muscle atrophy (n;%)	rhabdomyolysis (n;%)
Comirnaty®/ Tozinameran	5 492 *0.73% ° 2.7%	1 549 *0.21 °0.75	201	42	102662 *13.6 °49.9	3 838 *0.51 °1.9	278 *0.04 °0.14	5 796 *0.77 °2.8	118	205 *0.03 °0.1
SpikeVax®/ Moderna	1 692 *0.74% ° 2.5%	424 *0.19 °0.62	52	4	37 062 *16.3 °54.2	638 *0.28 °0.9	41 *0.02 °0.06	1874 *0.82 °2.7	46	127 *0.056 °0.19
Vaxzevria®/ AstraZeneca	5 438 *1.2% °3.2%	782 *0.18 °0,46	77	6	84744 *19 °50.1	1537 *0.34 °0.9	111 *0.02 °0.07	3875 *0.87 °2.3	67	47 *0.01 °0.03
Janssen	457 *0.9% °2.6%	69 *0.14 °0.4	8	2	11082 *22.2 °64.0	92 *0.18 °0.53	11 *0.02 °0.06	495 *1 °2.86	18	28 *0.056 °0.16

*% from individual cases; ° % of ADRs within the reaction group

Table 2. a) Suspected ADRs affecting the musculature (11.02.2022, (EudraVigilance, n. d.))

vaccine	Bell's palsy (n;%)	headache (n;%)	dizziness (n;%)	anosmia (n;%)	ageusia (n;%)	GBS (n;%)	peripheral sensorimotor NP (n;%)	PNP (n;%)	balance disturbances (n;%)
Comirnaty®/ Tozina-meran	2765 *0.37 ° 0.97	162907 *21.6 °57.4	47908 *6.35 °16.87	1820 *0.24 °0.64	2288 *0.3 °0.8	1130 *0.15 °0.4	63 *0.008 °0.02	351 *0.05 °0.12	2844 *0.38 °1.0
SpikeVax®/ Moderna	1592 *0.7 °1.7	54624 *24 °58.3	15724 *6.92 °16.8	492 *0.22 °0.52	706 *0.31 °0.75	420 *0.18 °0.45	13 *0.006 °0.014	76 *0.03 °0.08	924 *0.41 °0.99
Vaxzevria®/ AstraZe-neca	845 *0.19 °0.36	169179 *37.9 °71.9	36954 *8.3 °15.7	766 *0.17 °0.33	1728 *0.39 °0.73	1388 *0.31 °0.59	42 *0.009 °0.018	163 *0.04 °0.07	1806 *0.4 °0.77
Janssen	95 *0.19 °0.4	16435 *32.9 °69.3	3388 *6.78 °14.3	97 *0.19 °0.41	137 *0.27 °0.58	435 *0.87 °1.8	3 *0.006 °0.01	36 *0.07 °0.15	203 *0.41 °0.86

*% from individual cases; ° % of ADRs within the reaction group

Table 2.b) Suspected ADRs affecting the nervous system[1] (11.2.2022, (EudraVigilance, n.d.))

Headache (22-38% of individual cases, 57-72% of all side effects in the reaction group) and dizziness (6.4-8.3% of individual cases, 14.3-16.9% in the reaction group) were the most common. Unusually and relatively frequently, balance disorders appeared (n= 5 777; 0.39% from 1 478 143 individual cases), followed by Bell's palsy (n= 5 297; 0.36%), ageusia (n= 4 859; 0.33%), GBS (n=3 373; 0.23%) and anosmia (n=3 175; 0.21%). These symptoms are actually characteristic of Covid-19.

Polyneuropathies (PNP) were rarely recognized (Tab. 2. b). However, some PNP-related symptoms, such as paraesthesias (n=46 951; 3.2% on average related to all individual cases) or burning sensations (n=5 819; 0.39% on average related to all individual cases) were reported comparatively frequently (pl. see Table 2. c).

Numerous dysfunctions and disturbances of the central nervous system have been reported. In addition to the previously mentioned (pl. see Tab. 2. b and macrovascular heart-circulation disorders analysed in (Lehmann, 2021)), a considerable number of impairments in cognition, consciousness and attention (total n=10 579, 0.7%), as well as impairments of memory (total n=5 207; 0.35%) emerged (pl. see Table 2. c).

The EudraVigilance database provides a comprehensive overview of various organ system-related adverse events and associated fatalities. Thus, an initial risk signal can emerge in the event of an accumulation of unexpected reactions. In contrast, the association with the person affected by the side effects retreats the background.

On the other hand, the data compilation of the German Internet portal is patient-centered. An evaluation of the first data compilation is provided in Section 3.

vaccine	paraesthesia (n;%)	burning sensation (n;%)	altered state of consciousness (n;%)	cognitive disorder (n;%)	depressed level of consciousness (n;%)	distur-bance in attention (n;%)	memory im-pairment (n;%)	amnesia (n;%)
Comirnaty®/ Tozinameran	25829 *3.42 °9.1	3115 *0.41 °1.1	625 *0.08 °0.22	564 *0.07 °0.2	1290 *0.17 °0.45	3440 *0.46 °1.21	1539 *0.2 °0.54	986 *0.13 °0.35
SpikeVax®/ Moderna	5969 *2.63 °6.37	941 *0.41 °1.00	228 *0.1 °0.24	223 *0.1 °0.24	329 *0.14 °0.35	850 *0.37 °0.91	576 *0.25 °0.61	426 *0.19 °0.45
Vaxzevria®/ AstraZeneca	13605 *3.05 °5.78	1582 *0,35 °0,67	120 *0.03 °0.05	332 *0.07 °0.14	273 *0.06 °0.12	2006 *0.45 °0.85	792 *0.18 °0.34	715 *0.16 °0.3
Janssen	1548 *3.1 °6.53	181 *0,36 °0,76	14 *0.03 °0.06	47 *0.09 °0.2	22 *0.04 °0.09	216 *0.43 °0.91	99 *0.2 °0.42	74 *0.15 °0.31

*% from individual cases; ° % of ADRs within the reaction group

Tab. 2. c) Suspected ADRs affecting nervous system$_2$ (11.2.2022, (EudraVigilance, n. d.))

3. German data collection (German internet portal "nebenwirkungen-covid-impfung.org" (Nebenwirkungen der Covid Impfungen, n.d.); (Lehmann, 2022)).

3.a) General findings

In the first evaluation, 160 vaccinated individuals were analyzed. The ADRs of 112 cases (70%) were reported to health authorities.

Vaccinations were administered between January 26 and August 31, 2021. The Comirnaty® vaccine (61.9%) resulted in the most adverse event reports, followed by Vaxzevria® (23%), SpikeVax® (7.5%), Vaxzevria®/Comirnaty® (3.8%), Janssen from Johnson and Johnson (1.9%) and Vaxzevria®/ SpikeVax® (0.6%). The vaccine was not reported in 1.25% of cases.

The age of those affected was predominantly in the range of 30-49 years (59.4%); 94.4% were between 20-59 years of age. Significantly more women (75.6%) were affected than men (24.4%).

A total of 101 individuals (63%) had no comorbidities. A certain allergic/autoimmune predisposition among the affected persons was indicated by a total of 40 individuals (25%): 11 cases of Hashimoto's thyroiditis, 8 cases of hypothyroidism of unknown cause, 10 reported allergic predisposition, 7 had bronchial asthma, 2 had Sjögren's syndrome, one person reported an overcame PNP, and another reported vasculitis. Anamnestically, there were 12 cases of migraine, 9 cases of elevated blood pressure, one case each of diabetes type I and type II, 3 cases of glaucoma, 4 cases of gastrointestinal disturbances, 2 cases of heart-rhythm disturbances, four cases of arthrosis/rheumatic disease and five singular cases (stress-sensibility, mamma-Ca., tremor, karotydinie, sudeck/CRPS).

A total of 160 vaccinated individuals reported at least 608 suspected adverse reactions (ADRs) associated with spike-producing Covid-19 vaccination. The expected local reactions in the inoculation arm were not included in the analysis.

The recorded ADRs and calculated percentages did not reflect the complete spectrum of Covid-19 vaccine reactions. In this data collection, the focus was obviously on complaints, which are difficult to classify at first sight and are often categorized by

physicians as psychosomatic complaints or trivialities without recognizing a connection with the vaccination. The vast majority of cases referred to the peripheral and central sensorimotor nervous systems.

Of all reported symptoms, 67.5% were subjectively distressing, agonizing and in part severely impairing disorders of the peripheral/central nervous system and skeletal muscle system (see Tab. 3.). Death anxiety and panic attacks reported in individual cases (n=8, 5% of those affected), numerous emergency admissions (once: 7 cases, 3 times in two cases and 7× in one case), and hospital treatments (once: 4 cases, 2 times in 2 cases, 3 times and several times in one case each), as well as the accompanying sleep disorders (n= 17, see Tab. 3. A 7.) underlined the sometimes impressive severity of symptomatology.

Spontaneously reported, qualitatively different suspected adverse reactions	Number (n)	Percentage (%) from n= 608
A. Disorders of the neuromuscular and the nervous system		
1. a/b) paraesthesia/sensitivity disturbances	122	20.1
2. muscle pain/myalgia, - twitching, - weakness, -spasms, - atrophy, myokymia, myoclonus	82	13.5
3. dizziness	41	6.7
4. “brain fog”/disturbance in attention /depressed level of conscoiusness/memory impairment	36	5.9
5. headache/migraine	45	7.4
6. vision problems, visual impairment	36	5.9`
7. miscellaneous sleep disturbances	17	2.8
tinnitus	15	2.5
balance disturbances	2	0.3
death anxiety and panic attacks	8	1.3
taste disturbances/ageusia	4	0.7
sudden hearing loss	1	0.2
facial paresis/Bell’s palsy	2	0.3
	411	**67.5**
B. disturbances of the cardio-vascular system		
1. tachycardia, POTS	48	7.9
2. blood pressure increase	12	1.9
3. decreased blood pressure	5	0.8
alternating blood pressure	3	0.5
collaps	2	0.3
4. myocarditis	2	0,3
5. miscellaneous respiratory distress/asphyxiation attack	9	1.5
heart sensation/angina pectoris	5	0.8
arrhythmia	2	0.3
cardiac symptoms with pain of destruction	1	0.2
	89	**14.6**
C. skin reactions	**29**	4.8
D. gastrointestinal problems	**15**	2.5
E. general symptoms/miscellaneous weight loss	21	3.5
influenza/fever	17	2.8
weakness, floppiness, heavy legs	11	1.8
night sweats, sweating	10	1.6
Covid-19 disease (2 months after vacination)	**1**	0.2
menstrual irregularities	4	0.7
sum	**608**	

Table 3: Spontaneously reported, qualitatively different, suspected adverse reactions from the German Data Collection (Nebenwirkungen der Covid Impfungen, n.d.)

3. b) Paraesthesia/sensitivity disturbances

Paraesthesia/sensitivity disturbances (n=122, 20.1% of all reported side effects, (Table 3 A1.a/b) dominated the side effect profile. Typical were tingling, "ants walking", cold sensation, numbness and paralysis, stocking- or glove-shaped localization of the complaints (but also asymmetrical expression), pinprick/stinging or pricking sensations, burning, electrifying or stabbing pain and/or lightning-like shooting pain, partly of devastating character. These disorders often occurred in clusters in a single individual. All four Covid-19 vaccines were involved in the induction of this phenomenon.

Symptoms began immediately up to 5 min after the first application in some individuals (n=7). Seven individuals were affected 20-30 minutes later. However, most frequently, symptoms began one hour to 10-12 days after the first application (n=59). A comparatively late onset was noted in four cases each after 2 and 4 weeks. After the second vaccine application, the onset of symptoms was generally later: 2 × after 16 h, 5 × after 2-3 days, 1 × each after 4, 6, and 10 days, and 3 × after 1 week and once every 2 and 5 weeks. Occasionally, a wavelike course or relapsing recurrence of the symptoms has been reported.

These disorders are compatible with small fiber neuropathy (SFN) or vasculitic neuropathy. Only one patient (43-year-old man) with cardiovascular and neuropathic symptoms beginning 30 min after Comirnaty® was diagnosed with SFN.

Damage to the myelin sheath affects highly myelinated fibers and causes tingling and electrification and/or motor weakness, as well as slowed nerve conduction and decreased muscle autoreflexes. The predominant signs of paralysis are characteristic of Guillian-Barre syndrome (GBS).

Seven subjects (6 women and one man; 5 × after Comirnaty® and 2 × after AstraZeneca's vaccine) suffered dominant paralysis symptoms, 6 of them after initial vaccination. Three women showed signs of paralysis of all extremities. In the case of diagnosed tetraparesis after Comirnaty® vaccination, autoantibodies (AAK) against gangliosides were found. In one of the vaccinated individuals, massive symptoms appeared only after the 2nd vaccination. Demyelination was suspected in this case. One affected person reported complete paralysis for 10 minutes, which was diagnosed as a microvascular lesion.

Paralyzes were evident at 12 h to 3 weeks after vaccination. Five of the seven vaccinated patients experienced concomitant paraesthesias, such as tingling, numbness, or burning sensations. It is reasonable to assume that acute GBS of varying severity underlies these 7 cases.

31 vaccinated persons were searched for relevant autoantibodies (against β1, β2, α1, M2, M4, AT1, ACE2, MasR, Ang II, Ang 1-7), unfortunately no finding was noted in 20 cases. Five cases with positive autoantibody findings against AT1/ACE2 (out of 11 tested) involved 3 men (32, 32, and 43 years old; 2 × after Comirnaty®, 1 × after AstraZeneca) and 2 women (32 and 39 years old; 1 × after Comirnaty®, 1 × after AstraZeneca). Four of these patients showed both serious cardiovascular and neuropathic symptoms. In the fifth vaccinated individual, complaints were limited to the nervous system. In these selected vaccinated persons, the reactions started at the earliest after 15 minutes, 1 time on the day after vaccination, two times on the 3rd day, and 1 time on the 4th day. AAK against the Mas receptor for Ang 1-7 (vasodilatory, anti-inflammatory, and antiproliferative) were tested six times; in a 19-year-old patient with positive findings (according to AstraZeneca) and fever and chills as initial reactions, paraesthesia, pain, central nervous and gastrointestinal disturbances, and skin hemorrhages were added 14 days later.

3.c) Muscle complaints

Muscular dysfunctions, such as muscle pain/myalgia, twitching, cramps, weakness, and atrophy, was the second most frequent (n=82, corresponding to 51.3% of those affected). They often occurred simultaneously with paraesthesia and associated vegetative dysfunctions.

Muscle weakness was frequently observed (see Section 3. b). The complaints of weakness, floppiness, and heavy legs (n=11; see Table 3 E.) may also conceal a muscular disorder.

In the case of a 39-year-old woman who was severely injured by AstraZeneca's vaccine (dark urine and muscle wasting, reduction in exercise tolerance to approximately 15%, visual disturbances, and severe cardiovascular, skin, and gastrointestinal reactions), rhabdomyolysis should be considered.

Of the five cases with positive autoantibody findings against AT1/ACE2, as described in Section 3. b), all reported accompanying muscular symptoms (generalized twitching all over the body, vibration in extremities, and involuntary movement of limbs starting 3 days after Comirnaty®; muscle atrophy/dark urine ca. 10 days after AstraZeneca; muscle pain/double vision approximately 4 days after AstraZeneca; muscle twitching and cramping the day after Comirnaty®; weakness in extremities and unsteadiness of gait approximately 3 days after Comirnaty®). Spike-triggered dysfunction of ACE2 appears plausible in these cases.

3. d) Complaints of the central nervous system

Dysfunctions affecting the central nervous system showed a heterogeneous spectrum. Forty-five persons (28%) complained of headache/migraine, often of a stinging character, predominantly in the presence of other concomitant complaints, such as paraesthesia. In three persons, headache occurred within 30 min of the first dose, in five within 1-20 h, in 28 after 1-10 days, in four after 11 days to 6 weeks, and in three after the 2nd dose (16 h to 2 weeks). The cases described were reversible phenomena without progression to more severe disorders, such as stroke, cerebral infarction, and hemorrhage.

Dizziness was frequently reported (n=41; 25.6% of those affected). Often associated with dizziness were other symptoms

such as nausea, vertigo, ear noises/tinnitus (n=15; 9.4%), hearing loss (n = 1), and balance disorders (n = 2, see Tab. 3). "Brain fog" (concentration disorders/depressed level of consciousness/memory problems/impaired word finding) ranked third among adverse central nervous reactions with 22.5% (n=36) of those affected by side effects. The sensitivity to noise and/or light has occasionally been reported.

Visual disturbances (blurred vision, worsened vision, visual acuity reduction, visual blur, visual difficulty; focusing problems 3×, double vision 1×) were considered very distressing, often interfered with occupation, and occurred frequently (n=36, about 22.5% of n=160). Comirnaty® was most frequently involved (n=24), followed by Vaxzevria® (n=9) and Moderna (n=3). Most reactions occurred after the first dose (n=32; 6 × within up to 5 h, 17 × up to 1 week, 7 × up to 4 weeks, and once every 6 weeks and 5 months, respectively), and 4 after the 2nd dose (3 days to 2 weeks). In one case, observed after the first and the second doses, there may be an association.

Taste changes (4 = 2.5%) and facial paralysis (2 = 1.3%) add unusual and transient impairment of the two cranial nerves (facial and glossopharyngeal nerves) to the spectrum of spike-induced nervous system side effects.

3.e) Cardiovascular disturbances

The most frequently reported symptoms were palpitations (pulse up to 180 beats/min) or postural tachycardia syndrome (POTS; n=48, 30%, Tab. 3. B 1.), which occurred in 71% of the cases in association with paraesthesia. Symptom onset varied from immediately after vaccine application to 15 min (n=10; concomitant with paraesthesia in 4 cases), 1-10 hours (n=6), 1-10 days (n=21), 11-20 days (n=1), and one case that occurred after 4 weeks. This symptomatology was reported 6 times after the 2nd dose (3 days to 5 weeks). POTS occurred once 3 days and once 2 weeks after the 2nd dose together with other polyneuropathic disorders. 2 cases of arrhythmias (Tab. 3. B 5.) were added to the symptomatology.

Blood pressure increases were reported by 12 persons (= 7.5%). With the addition of another 60 reports (from 220 individuals), the number of blood pressure elevations increased to 22 (10%). The blood pressure rises began immediately after vaccination or on the first day in seven cases; blood pressure values were at threatening levels between 205/99 and 215/115 mm Hg in two of those vaccinated. Elevated blood pressures were noted in eight vaccinated persons between days 2-6 after the first vaccination, in one person on day 9, and in four between days 3 and 4 after the second dose. In two cases, the onset was not noted. Two subjects reported increases in blood pressure after both the first and second doses, which is a strong indication that vaccine spikes may be responsible.

A decrease in blood pressure was less frequent than an increase in blood pressure among the 220 vaccinated persons (9=4.1%). It was observed in 3 cases 10 min to 1 h after vaccination, in 4 subjects between vaccination day and day 3 after vaccination, and in 2 subjects after the 2nd vaccination.

Alternating blood pressure was reported in four cases (immediately to 10 days after vaccination). Circulatory collapse was noted in two cases (45 min and on day 1).

Myo/pericarditis was diagnosed in 4 (1.8%) of the 220 vaccinated individuals. Affected were two women, aged 43 and 25 years, who became ill 5 days after the first dose and 14 days after the second dose, and two men, aged 43 and 25 years, respectively, who became symptomatic 30 min after the first dose and 4 days after the second dose. All received Comirnaty®.

Respiratory distress/asphyxiation attack (n=9; 5.6%) occurred in combination with sensorimotor and central nervous symptoms, as well as in association with cardiovascular reactions, mostly on the same day or up to 2 weeks after vaccination. They characterized the severity of the primary causative symptomatology.

Heart sensation/angina pectoris (n=5; 3.1%) and cardiac symptomatology with pain of destruction (n=1; 0.63% immediate onset) were warning symptoms of spike-induced impaired coronary blood flow.

3.f) Skin reactions

Skin reactions, such as petechiae or bruising/hemorrhages (n=12), hemangiomas, rash, increased spider veins, redness, blue discoloration, and/or skin peeling (n=14 reactions) were troubling and distressing. Lip herpes (1 case; 0.63%) or other herpes infections (2 cases; 1.3%) were rarely observed.

They always occurred in association with complex complaints and were usually clustered. The earliest onset occurred at 12 hours (n=1). Most skin symptoms started between 2 days to one week (n=21), 1 × after 10 days, 1 × each after 2, 3 and 9 weeks. Moderna elicited the most frequent reactions (n=12), followed by AstraZeneca (n=10), and Comirnaty® (n=4).

3.g) Further complaints

Gastrointestinal problems (n=10; 6.25%) and diarrhea (n=5; 3.1%) complete the spectrum of commonly reported suspected side effects.

General symptoms, such as weight loss (n=21; 13.1% of those affected by side effects), weakness/floppiness/heavy legs (n=11; 6.9%), and night sweats/sweating (n=10; 6.25%) did not have an autonomous disease value and were assessed as accompanying symptoms of severe neuropathic, muscular, and/or cardiovascular primary disorders.

Influenza/fever (n=17; 10.6%), although known to be a vaccine consequence, should be considered separately in the context of increasing vaccine breakthroughs.

Menstrual disorders (n=4; 2.5% of those affected by side effects) and the occurrence of Covid disease (n=1; 0.63%) among vaccinated individuals require further clarification.

Discussion

The worrisome trend of an increase in the broad spectrum of Covid 19 vaccine-associated adverse events has continued since the vaccination campaign began in late 2020. However, the overall average ADR-lethality has not changed since June 2021, remaining constant at a relatively high level of approximately 2.6%. This surprisingly high ADR-lethality could be due to the preferential reporting of particularly serious reactions. On the other hand, considerable under-reporting must be conceded for various reasons (reporting laziness, unawareness of a correlation), as already mentioned on several occasions.

SpikeVax® experienced a particularly significant increase in ADRs (to 210% since June 2021); adverse events were most frequently fatal after SpikeVax® and Janssen vaccination (4.75% and 4.9%, respectively). However, the increasing trend of individual cases with adverse events through mid-February 2022 was most pronounced for the most commonly used vaccine, Comirnaty®.

Safety-related restriction of use generally results in a significant reduction in side effects, even if the reduction in frequency of use is not precisely known, as shown by the example of Vaxzevria®. Recognition of thrombo-embolic events and, some time later, GBS, CLS, and cases of transverse myelitis significantly limited the use of Vaxzevria® as of May/June 2021. There was a significant reduction in adverse reactions from 21116/day (Lehmann, 2021), to 1196/day or to 736/day, respectively, when only the time period between June 6, 2021, to February 13, 2022, was compared with the cumulative frequency up to June 5, 2021.

In contrast, Comirnaty® experienced no trend reduction in terms of increase in ADRs and apparently no market decline until January 2022, despite the known risk of peri-/myocarditis. This phenomenon has not yet been interpreted and could be due to the downplay or trivialization of this dangerous vaccination side effect.

Disorders in the reaction group "general disorders and complaints at the administration site" (EudraVigilance, n.d.), which subsumes most of the adverse effects of the vaccine referred to as "reactogenicity", were the most frequent (but not analyzed here), followed by disorders of the nervous and musculoskeletal system. This review/analysis provides the first impression of numerous adverse events associated with Covid-19 vaccination that have received little attention to date and, are often unexplained, but are nevertheless highly debilitating.

16.2-20.2% of all spontaneously reported ADRs were related to the nervous system and 11.7-14.5% involved the musculoskeletal system according to the Web reports of EudraVigilance. Unexpectedly, nervous system disorders ended fatally with a significant frequency (9.4-14.7% of all fatal adverse events). This is in the same range as fatal adverse events in the respiratory system (10.6-13.7%) and cardiac system (8.4-14.5%, Table 1.b), signaling a significant severity. The only slightly differing frequencies do not indicate a different mode of action, but rather class-specific effects.

In German data collection (Nebenwirkungen der Covid Impfungen, n.d.), side effects affecting the nervous and musculoskeletal system were mentioned more frequently (67.5%). Symptoms of the peripheral nervous system, which are unusual for conventional vaccines, such as tingling, "ants walking", cold sensation, numbness and paralysis, pinprick/stinging or pricking sensations, burning, electrifying or stabbing pain and/or lightning-like shooting pain, seem to have caused a certain helplessness among the treating physicians in many cases. Unsuccessful attempts at treatment without prior diagnosis prolonged the suffering of those affected, so they tried to exchange information with each other, which led to this collection of data.

Nevertheless, surprisingly both data sources provided consistent information. Among those affected, there were generally more women (55-76%) than men (24-42%), who were predominantly between 20-59 or 18-64 years old (76-94%, (EudraVigilance, n.d.); (Nebenwirkungen der Covid Impfungen, n.d.)). The patient's symptoms were similar.

However, the relative frequencies in the overall spectrum of reported adverse events can only be obtained from the EudraVigilance Web Report. By contrast, German data collection is much more suitable for characterizing specificity.

Diagnosed paraesthesias and sensitivity disorders were common (2.6-3.4%, on average 3.2%, related to individual cases; Tab. 2. c). Symptoms of sharp pain, burning sensation, disturbed pain, and temperature sensation (hyperesthesia) are characteristic of impairment of low- myelinated and unmyelinated fibers of the peripheral nervous system. If blood supply to these fibers is interrupted or disturbed after vasculopathy, for example, vasoconstriction or vasculitis, peripheral nerve dysfunction may occur, including the symptoms described. Impairment is usually asymmetric at the onset and often begins in the distal third of the extremities. These disorders are compatible with small fiber neuropathy (SFN), and vasculitic neuropathy in the presence of underlying vasculitis. Both are subtypes of polyneuropathy, which has very rarely been recognized (only in 0.03-0.07%, Tab. 2. b). This under-recognition must be improved through increased educational efforts.

Tingling and electrification and/or motor weakness, as well as slowed nerve conduction and decreased muscle intrinsic reflexes, are typical impairments of highly myelinated fibers (Rubin, M, 2019_1). Demyelination or damage to the myelin sheath and/or axonopathy characterize Guillain-Barre syndrome (GBS: acute inflammatory demyelinating polyneuropathy), and may be the most common acquired inflammatory neuropathy (Rubin, 2019_2), a consequence of an exaggerated autoimmune reaction with antibody formation against glycolipids of the myelin sheaths (Ritschel, et al., 2021); (Deutsche Gesellschaft für Neurologie, 2020), or T-cell activation (Malin & Sindern, 1996).

GBS has been observed relatively frequently in European countries (in 0.2 up to 0.9% of all individual cases, Tab. 2.b). In the German PEI authority safety report (through 11/30/2021(Security Report, 2021)), the occurrence of GBS was noted in 314 cases associated with Covid-19 vaccines, but only 160 cases were attributed to vaccination and only to vector vaccination. The remaining cases (n=154) were considered irrelevant. However, the data presented here demonstrate that a mean GBS incidence of less than 0.2% (0.15-0.18%) for mRNA vaccines should certainly be considered a vaccine-associated adverse event. In addition, the manufacturer BioNTech/Pfizer was aware of this dangerous side effect as early as February 28, 2021 as a cause for concern (5.3.6 CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT REPORTS OF PF-07302048 (BNT162B2) RECEIVED THROUGH, 2021).

The syndrome is known to occur after vaccination (Rubin, 2019_2); (Guillain Barré Syndrom, 2021) as well as after SARS-CoV-2 infection (Ritschel et al., 2021); (Deutsche Gesellschaft für Neurologie, 2020); (Tawakul et al., 2022); (Hasan et al., 2021) or other infections. Patone et al. (Patone, et al., 2021) found an increased risk of GBS and hospitalization after Vaxzevria® but not after the BioNTech vaccine. No explanation for the difference was provided. Tawakul et al. (Tawakul et al., 2022) recently submitted an interesting explanation for the association between Covid-19 infection and the occurrence of GBS. The SARS-CoV-2 viral antigen, the spike glycoprotein, may lead to an autoimmune response because of its structural similarities with the ganglioside components of peripheral nerves, thereby damaging them. The same explanation applies to GBS causation due to spike-producing Covid-19 vaccines. In the case of tetraparesis, this hypothesis was confirmed by detection of auto-antibodies against gangliosides. Past GBS disease does not appear to increase the risk of vaccine-induced GBS (Shapiro et al., 2021).

In most cases, however, paraesthesia and sensory disturbances are likely to have in common a reduced blood supply via the vasa nervorum, triggered by vasoconstriction and/or inflammatory reactions of the small nerve-nourishing vessels (vasculitis). Vasoconstriction is probably due to an activated RAAS after impairment of counterregulatory vasodilatory and vasoprotective ACE2 action by spikes. Unfortunately, microvascular supply and markers of activated RAAS have not been systematically studied, but disturbance was suspected in one case of transient paralysis.

In some cases of neuropathy in the German data collection (n=5), auto-antibodies against AT1/ACE2 were found. Together with the findings of antibodies against the Mas receptor (n=6), there is compelling evidence of the causal involvement of a disturbed ACE2/MasR axis in triggering neuropathic symptoms.

The second most common peripheral disorders involved the musculo-skeletal system. Symptoms often occurred concomitantly with paraesthesia and associated autonomic dysfunction and can be classified as symmetric sensorimotor manifestation type (Heuß, 2019) or, as multifocal motor neuropathy in the absence of sensory impairment (MMN, (Schlotter-Weigel, n.d.)). In addition to distally accentuated asymmetric motor muscle weakness/paresis, typical symptoms of MMN include diffuse muscle pain, muscle spasms, sometimes generalized fasciculations, myokymia, and muscle wasting, which have been reported very often (Tab. 2. a). In rare cases, mild sensory disturbances may accompany muscle disturbances, suggesting a diagnosis of multifocal acquired demyelinating sensory and motor neuropathy (MADSAM). Because of frequent occurrence of antibodies, an immune-mediated genesis is suspected in these disorders (Schlotter-Weigel, n.d.); (Multifokale motorische Neuropathie, n.d.). Disturbances in muscle function have also been discussed in the context of vasculitides (Schlotter-Weigel, n.d.) or as a consequence of a Covid-19 systemic multi-inflammatory syndrome (MIS A, (Keymel, 2022)).

Muscle pain/myalgias are common in Covid-19 disease (Hasan et al., 2021) and usually resolve within a few days. The myalgias seen in association with the spike-based vaccines were in a similar range (14-22% vs. 19% in Covid-19 patients), pointing to a common pathogenesis in these cases. The basis for a direct effect of spikes on muscle cells would be the presence of the membran-bound receptor enzyme ACE2. This has been demonstrated (Han et al., 2020). Therefore, a direct spike effect on the musculature can be considered at least partially causative. Vascular endothelia also contain ACE2, so the supplying blood vessels may contribute to muscle injury after spike action. Inflammatory reactions to spikes may also be involved in the development of myalgia.

Some unusual and worrisome symptoms, such as myokymia or myoclonus, occurred both after spike-based vaccine application and during a Covid-19 disease (Khan et al., 2021); (Lehmann et al., 2021); (Torrealba-Acosta et al., 2021). Myokymia, among numerous other adverse events, was previously identified as an adverse event of special concern by BioNTech/Pfizer on 28 february 2021 (5.3.6 CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT REPORTS OF PF-07302048, 2021). These occurrences in Covid-19 disease patients as well as after Covid-19 vaccination, suggest that analogous (vascular-/nerve-) muscle pathology is present.

Muscle weakness and spasms were reported relatively frequently (0.7-1.2%), and less frequently muscle twitching, paresis, or atrophy. The etiology is unknown, but disturbed blood supply and/or impaired nerve/muscle transmission may be causative factors. Covid-19 also been known to cause neuromuscular damage, particularly in critically ill patients (Hasan et al., 2021). One of the essential proposed mechanisms is the interaction between SARS-CoV-2 and the receptor enzyme ACE2, which is expressed in many tissue types, including musculature, smooth muscle, synovial tissue, and cartilage. Inflammatory molecules, such as IFN-γ, IL-1β, IL-6, IL-17, and TNF-α, are known to directly impact skeletal muscle by inducing fiber proteolysis and decreasing protein

synthesis. These inflammatory molecules may be involved in triggering decreased muscle strength and endurance (Hasan et al., 2021). If the anti-inflammatory and vasodilatory properties of ACE2 are limited by SARS-CoV-2 or isolated spikes, adverse consequences for normal muscle activity are expected. Rhabdomyolysis, a syndrome characterized by skeletal muscle injury and necrosis that presents with myalgia, weakness and dark urine, was found in 0.03% (n=407) of all cases with side effects. Approximately 10 days after vaccination with Vaxzevria®, typical symptoms were described by one affected individual from the German data collection without a diagnosis of rhabdomyolysis. The first case was published along with a literature review in August 2021 (Nassar et al., 2021). Rhabdomyolysis has been diagnosed in several cases after infection with SARS-CoV-2. Etiologies included medications, infections, and inflammatory myopathies, among others, in addition to ischemia or hypoxia (Nassar et al., 2021). Although the occurrence of rhabdomyolysis associated with Covid-19 vaccination is rare, clinicians should be vigilant of the possibility of this muscle disorder associated with Covid-19 vaccination, as early diagnosis and treatment have an excellent prognosis.

Of the five cases reported earlier with positive auto-antibody findings against AT1/ACE2, all reported accompanying muscular symptoms (generalized twitching throughout the body, vibration in extremities, and involuntary limb movement beginning 3 days after Comirnaty®; muscle atrophy/dark urine approximately 10 days after Vaxzevria®; muscle spasms, double vision approximately 4 days after Vaxzevria®; muscle twitching and cramping the day after Comirnaty®; weakness in extremities and unsteadiness of gait approximately 3 days after Comirnaty®). Spike-induced dysfunction of ACE2 seems plausible in these cases.

Headache/migraine is a common everyday phenomenon that occurs in response to various systemic, regional, or local events. Headache occurs in up to one-third (Schlenger, 2020) of Covid-19 patients and in up to 65% of vaccinated patients after Moderna/SpikeVax® or Comirnaty® (Göbel et al., 2021); (SpikeVax®. n.d.).

The incidence based on spontaneously reported cases in this analysis was lower, averaging 27.3% (21.6-37.9%; EudraVigilance; Table 2.b) and approximately 28%, respectively (German data collection; Table 3. A 5.). The cases described were reversible phenomena without progression to more severe macrovascular disorders, such as stroke, cerebral infarction, hemorrhages, or others. The character of the headache was sometimes stinging, flash-like, usually in combination with other complaints, such as sensitivity disturbances, and often persisted for weeks.

The relatively common reversible cerebral vasoconstriction syndrome (RCVS, (Leitlinien für Diagnostik und Therapie in der Neurologie, 2018)) produces quite similar symptoms - attack-like thunderclap ("Donnerschlag") headache with subliminal persistent dull headache. Angiographic evidence of vasospasm can be obtained using the vasodilating cacium channel blocker, nimodipine. Triggers include vasoactive substances such as catecholamines and angiotensin II (Leitlinien für Diagnostik und Therapie in der Neurologie, 2018). In cases of regional dysfunction of ACE2 by virus-spikes or spike-based vaccines, their effects may be enhanced. ACE2 has been known to be expressed in the brain since approximately 2005 (Xia & Lazartigues, 2008). A direct interaction of the spikes produced by vaccination, as well as the viral spikes, with the ACE2 receptor present in the brain tissue, is suggested. RCVS has been repeatedly reported as a complication of SARS-CoV-2 infections (Arandela et al., 2021). It is therefore not surprising that the first case of reversible cerebral vasoconstriction syndrome was recently observed after SARS-CoV-2 vaccination (Finsterer, 2021). Interestingly, the affected woman did not suffer from scotomas and thunderclap headaches until 18 days after the second administration of Moderna. Acute cortical ischemic lesion could be detected using MRI. Cerebral vasculitis was among the conditions that were excluded. Nimodipine was therapeutically effective. Therefore, the hypothesis of vasoconstrictive causation seems to be most plausible.

Vascular constriction followed by tissue ischemia may be complemented in affected regions by immunological-proinflammatory as well as hypercoagulatory sequelae, as known from SARS CoV2 infections (Arandela et al., 2021).

Dizziness was frequently communicated (up to approximately 26%). This is consistent with the findings of other authors who noted dizziness as one of the most frequently observed reactions after Covid-19 vaccination (21%, (Gianfredi et al., 2021). In 2022, 33 cases of acute vertigo were reported for the first time (Di Mauro et al., 2022), occurring within 48 h of vaccination, most frequently after the BioNTech vaccine (n=23). Frequently, other symptoms, such as nausea, ringing in the ears/tinnitus, hearing impairment/loss of hearing, and balance disorders, have been associated with dizziness. Dizziness/vertigo may be secondary to orthostatic hypotension, blood pressure fluctuations, or cardiac arrhythmia/tachycardia, and thus is related to sensorimotor/vegetative neuropathy.

Disturbances of the blood supply and/or immunological reasons can be an additional important factor. Because the vestibular organ of the inner ear is particularly sensitive to impaired blood supply, vascular constriction, vasculitis, or endothelial dysfunction can trigger symptomatic circulatory disturbances. Again, dysregulation of the ACE2/RAAS axis may be a causative factor. ACE2 and TMPRSS are present in the inner ear, and SARS-CoV-2 has been shown to affect certain inner ear cells (Jeong et al., 2021). Crossing the blood-brain barrier is considered a precondition for the central nervous activity of SARS-CoV. This has been known since 2008 and was also demonstrated for subunit S1 of SARS-CoV-2 in 2021 by adsorptive transcytosis in mice. Murine angiotensin-converting enzyme 2 is involved in brain and lung uptake (Rhea et al., 2021). In addition to ACE2, other receptors for SARS CoV2/spikes are under discussion (Rhea et al., 2021);

(Erickson et al., 2021); (Datta et al., 2021).

Also, cross-reactions of antibodies or T-cells that misidentify inner ear antigens as viruses are capable of causing damage as well (Di Mauro et al., 2022). An association between vaccination and the side effect dizziness seems plausible.

The term "brain fog" characterizes clouding of consciousness or cognitive deficits and is used for Covid-19 symptoms, but increasingly also for the same symptoms occurring after Covid-19 vaccination.

It is well recognized that a lack of oxygen (hypoxia) in the brain can lead to symptoms such as transient memory loss, problems with body part coordination, inattention, poor judgment (Karuppan et al., 2021), and disruption of the blood-brain barrier function (Erickson et al., 2021). These phenomena have been reported in association with Covid-19 infections. Viral particles could be detected in endothelial cells of the brain, neurons, and various brain regions of deceased critically ill patients (cited in (Erickson et al., 2021)). Wenzel et al. (Wenzel et al., 2021) recently found a significant increase in empty basement membrane tubes (string vessels) remaining after the death of vascular endothelial cells in the brain tissue of Covid-19 infected individuals. The apoptosis marker caspase 3 was significantly increased in the small blood vessels. Cell death was considered to be a consequence of SARS-CoV-2 infection. According to the authors, brain endothelial cells are disproportionately at risk for SARS-CoV-2 infection. Consequently, SARS-CoV can damage endothelial cells and neurons, and contribute to their apoptosis (Erickson, et al., 2021). In milder disease courses, evidence exists for the involvement of the blood-brain barrier (Erickson, et al., 2021) in the case of prostaglandin E2-dependent fever, cytokine-accompanying increased feeling of illness, IL-1alpha-impaired memory processes, and kynurenine production accompanying inflammatory reactions, which facilitates depressive states.

In testing the hypothesis that the S1 protein of SARS-CoV-2 can directly induce neuronal injury, Datta et al. (Datta et al., 2021) demonstrated that the exogenous S1 protein leads to endolysosomal dysfunction and dystrophy of neurons. These processes can also disrupt the transport of synaptic vesicle precursors, lysosomes and autophagic components (Datta et al., 2021). The authors correctly suggested that S1 is involved in the high incidence of neurological and psychological manifestations of SARS-CoV-2 infection. However, they doubt that the specific effect of endolysosome deacidification involves the ACE2 receptor-binding domain, so the current mRNA vaccines for Covid-19, which encode the full-length S protein, are not affected. The precise mechanism by which endolysosomal dysfunction is induced remains unclear. In any case, there is no doubt that cell entry requires the ACE2 receptor, and numerous central nervous disorders have been reported after Covid-19 vaccination

Visual disturbances are usually uncommon after conventional vaccinations. The visual disturbances observed up to one week may be caused by microvascular supply disturbances of the retina and/or visual center after spike exposure. Acute visual disturbances with retinal hemorrhages have been reported in association with Vaxzevria® vaccination and auto-immune thrombocytopenia (ITP) (Bachmann et al., 2021).

Changes in the sense of taste and smell, and facial nerve palsy are common sequelae of Covid-19 infection (Gupta et al., 2020), but as is now known, are also sequelae of Covid-19 vaccination.

The remarkable frequency of facial paralysis (0.2-0.4%) among vaccinated individuals with ADRs supports a causal relationship between spike-based vaccination and facial paralysis. Patone et al. (Patone et al., 2021) reported that facial paralysis occurred simultaneously with GBS after Vaxzevria®. Autoimmune processes, such as a mononeuritic variant of GBS, have been implicated as causative factors for facial nerve palsy.

Since infections with SARS-CoV, their neuroinvasive and neurotropic effects are known. Gupta et al. (Gupta et al., 2020) mentioned that the nasal epithelium has the highest ACE2 expression of the respiratory tract. Besides, the olfactory epithelium is discussed as a portal of entry for the transsynaptic transmission of SARS-CoV-2 viruses to the brain. While these facts have direct relevance to Covid-19 complications. However, this route of transmission cannot be considered for vaccine spikes. The only explanation for the same symptoms observed after vaccine application is that the spikes formed in the body of the vaccinated person are distributed systemically and find their receptor far from the site of injection to exert their harmful effects. The exact mechanism underlying the impairment of function of the two cranial nerves, N. facialis and N. glossopharyngeus, is unknown. Transient microvascular supply disturbances after vasoconstriction, similar to those described in the peripheral nervous system, should be included in the discussion of the causation.

The cardiovascular disorders recorded in the German data collection are not representative of the complete spectrum of cardiovascular adverse events reported to date. Notable is the absence of serious, partly life-threatening symptoms, such as myocardial infarction, angina pectoris, heart failure, transient cardiac arrest, stroke, infarctions of various locations (brain, kidney, mesenteric arteries, etc.), embolisms (e.g., pulmonary embolisms), or thromboses with predominantly macrovascular or mixed macro/microvascular etiology that required immediate medical attention. The first analysis of these post-vaccination events was published in August 2021 (Lehmann, 2021).

The cardiovascular symptoms presented here (palpitations, POTS, blood pressure decrease, alternating bp) correspond, in principle, with the exception of blood pressure elevations and crises, to the complex of polyneuropathic diseases with neurovegetative components already mentioned. The immediate onset of symptoms within a few minutes after vaccination

suggests allergic genesis, and the onset of symptoms after days to weeks suggests a slower developing process, for example, a reaction to an escalating inflammation of the small vessels and/or the development of autonomic neuropathy.

Recent studies have demonstrated that spike glyco-proteins are capable of damaging the vascular endothelium in response to a dysregulated renin-angiotensin system triggered by ACE2 downregulation or loss (Lei et al., 2021). ACE2 is particularly high expressed in pericytes (wall cells of capillaries and small blood vessels) of healthy cardiac muscle but not in cardiac nerve fibers (Robinson et al., 2020). In the presence of spikes, the protective role of ACE2 cannot take effect, and therefore, the pathophysiologically deleterious Ang II effects, such as vasoconstriction, hypertrophy of cardiomyocytes, tissue fibrosis, increased oxidative stress, inflammation, and blood clotting, predominate. This may manifest as increased blood pressure, circulatory disturbances/coronary heart syndrome/heart attack, myocardial damage/heart failure, and tachycardia/arrhythmias.

Alarming increases in blood pressure were reported by approximately 10% of vaccinated individuals. The close temporal relationship between blood pressure increase and vaccination (predominantly within the first few days) indicates spike-activated vasoconstriction. Recognition of this almost classical relationship between restriction of the vasodilator/vasoprotective ACE2/MasR axis by spike action and reactive increase in blood pressure depends on the attention and knowledge of vaccinators. These may vary widely and may be an important reason for the variation in frequency of reporting. In addition to the peripheral dependence of blood pressure regulation on the RAAS and its counterregulation, elevated blood pressure can also be caused by central regulatory derailment in the brain regions responsible for it, such as the brainstem or hypothalamus, in a complex interaction system involving multiple local and systemic components (Xia & Lazartigues, 2008). The Mas receptor, which is highly expressed in the brain, may be considered as one of the regulating links. ACE2 appears to be more important than ACE in normal brain function and acts as a compensatory limiting mechanism of RAAS hyperactivity (Xia & Lazartigues, 2008). Absence or dysfunction of ACE2 results in increased sympathetic tone and decreased parasympathetic tone, which may manifest in the periphery, for example, by tachycardia and elevated blood pressure. Initial experimental attempts to selectively stimulate ACE2 (xanthenone, resorcinol naphthalein), thereby enhancing its RAAS-attenuating effect, resulted in lowered blood pressure and improved cardiac function, as expected (Xia & Lazartigues, 2008). This led to the conclusion that the influence of vaccine spikes on ACE2 is causally involved in blood pressure regulation.

Myo-/pericarditis is as a recognized side effect of mRNA vaccines. However, the number of cases reported to date does not indicate an exclusive relationship between mRNA vaccination and myocarditis. mRNA vaccines had higher rates than vector vaccines, but vector vaccines appear to be more dangerous in terms of fatal outcome of myo/pericarditis (1.27-5.56% vs. 0.85-1.04%, (Lehmann, 2021). In addition, in the context of the known potential causative factors, viral infection, vaccination, and non-infection causes, a class-specific side effect of spike-based vaccines was obvious from the beginning. In particular, the spike/ACE2 interaction suggested causality.

Spike-based vaccines share the ACE2 receptor, which is expressed in human cardiomyocytes, endothelial cells, and cardiac pericytes (Huber, 2021), as well as in every known cell type. Although a few other receptors for viral cell entry have been found (e.g., neuropilin 1, CD147 (Wang et al., 2020), both the extensive Covid-19 clinical picture and the unusually broad spectrum of side effects of spike-based vaccines can be explained predominantly by ACE2-downregulation. Spike-induced loss of ACE2 activates the renin-angiotensin system, resulting in Ang II/NA-dependent acute vasoconstriction and the progression of inflammatory, fibrotic, and thrombotic processes.

Evidence for the participation of AngII/NA is provided by the clarification of the sudden death of two teenage boys after the second BioNTech vaccination (Gill et al., 2022). Histopathological examination revealed stress cardiomyopathy caused by catecholamines, which was different from typical myocarditis findings. Without explicitly mentioning of spike/ACE2 interaction, the authors included epicardial spasms and microvascular dysfunction as well as direct toxic effects on cardiomyocytes as causation for catecholamine-induced myocardial injury (Gill et al., 2022). Evidence of hypersensitivity reaction could not be provided. However, the fibrosis detected in one case appears to be consistent with the pattern of RAAS-induced subacute sequelae.

A completely different explanation for the occurrence of myocarditis after immunization was provided by Sloop et al. (Sloop et al., 2021). They hypothesized that inflammation increases blood viscosity, followed by decreased myocardial perfusion and supply. This can be prevented by optimal oral hydration. On the other hand, the renin-angiotensin-aldosterone system is the main regulatory mechanism of renal sodium excretion and thus, the volume balance of the body. Hemoconcentration is prevented by Na/and water reabsorption, and this should work in the case of a Covid-19 infection or vaccination.

In addition, skin efflorescences starting up to one week could be related to impaired ACE2 activity due to spikes. It is known that all components of the RAAS required for Ang II synthesis are present in vessels that nourish the skin as well as in cutaneous cells. AT1 and AT2 receptors were also detected. The skin is capable of Ang II formation independently. It has been postulated that the physiological role of the skin RAAS is to regulate keratocyte proliferation and differentiation, which can be derailed under pathological conditions (Wollschläger, 2005). Coronavirus particles have been detected in the cytoplasm of capillary epithelial cells (Ricke, 2021). Magro et al. (Magro et al., 2021) detected spike glycoprotein and ACE2 in the

endothelium of skin microvessels in all vaccinated individuals tested with generalized skin efflorescences. Therefore, the hypothesis of ischemia after vasoconstriction with subsequent mast cell hyperactivity is plausible.

Immunologic reactions are thought to be due to foreign mRNA as well as after dysregulation of local RAAS (IL-6, etc.) as a consequence of ACE2 dysfunction. Immune thrombocytopenia (ITP), which is known in Covid-19 patients, can initially be recognized by petechiae, hemorrhages or purpura of the skin or mucosa. Increased platelet degradation and reduced production are detectable; platelets become coated by anti-platelet antibodies and immune complexes, resulting in their elimination by phagocytes (Seneff & Nigh, 2021). Thus, the frequency of skin hemorrhages, bruises, and petechiae (n=12) in the data collection finds an explanation.

The gastrointestinal disturbances after Covid-19 vaccination, as well as all other side effects observed, show a qualitative similarity to the symptomatology of Covid-19 infection and support an impression of the unusually broad spectrum of side effects of these types of vaccines. Covid-19 infected individuals suffer from intestinal symptoms and diarrhea (Gheblawi, et al., 2020) related to the expression of ACE2 in the gut. It is known for some time that ACE2 is highly expressed in the gut (Han et al., 2020). However, ACE2 exerts a RAAS-independent function in the intestine. This process regulates intestinal amino acid homeostasis. Therefore, it influences the gut microbiome. Intestinal dysbiosis and altered intestinal permeability have been shown to be important mechanisms of diseases controlled by the ACE2 axis (Lehmann, 2021), such as vascular and pulmonary diseases and diabetes mellitus.

Because of the presence of ACE2 on the entire inner intestinal surface, especially the enterocytes, the intestine is considered a secondary site of manifestation of SARS-CoV-2 virus infection.

Conclusions

Adverse reactions to the novel conditionally authorized Covid-19 vaccines are unusually various and frequent compared with other conventional vaccines and are associated with considerable lethality. The worrisome trend of an increase of adverse reactions is unbroken. It is noteworthy that the only slightly different frequencies of adverse events and fatal outcomes between mRNA and vector vaccines provide the first indication of the class-specific effects of spike-based vaccines. The results of this analysis document, for the first time, frequently observed suspected organ-related adverse events in the peripheral and central nervous systems, musculature, and skin which can be attributed to a common pathogenesis following vaccination. This spectrum was complemented by typical cardiovascular reactions, as has been extensively analyzed previously.

The most substantial cause of the adverse reactions is the spike/ACE2 interaction, which is inherent in both SARS-CoV-2 and spike-based vaccines. The spike glycoprotein subunit S1 binds with its RBD to the extracellular domain of the receptor molecule ACE2 and causes its dysfunction. Because of the key role that the enzyme ACE2 plays in the physiologically extremely important renin-angiotensin-aldosterone system (RAAS), its dysfunction may result in numerous pathophysiologically harmful reactions. Auto-antibodies may also be involved, but their presence and development require further investigations In the presence of spikes, the protective role of ACE2 is down-regulated or suppressed in almost all known cell types in which it is expressed, particularly in brain, cardiomyocytes, pericytes, endothelial cells, muscle cells, skin, and intestine, and pathophysiologically deleterious Ang II/NA effects predominate, such as increased sympathetic tone, vasoconstriction, hypertrophy of cardiomyocytes and smooth muscle cells, tissue fibrosis, increased oxidative stress, inflammation, and blood clotting. The most obvious manifestation of this almost classic physiological relationship is an increase in blood pressure, including a hypertensive crisis. Catecholamine-induced stress-cardiomyopathy should be considered in cases of sudden cardiac death. These effects are primarily mediated by the vascular system.

In addition, some evidence has been found for spike-induced neuromuscular disorders (myalgia, pain, spasm, generalized muscle twitching, myokymia, weakness, paresis, rhabdomyolysis), nervous system disorders (paraesthesia, sensitivity disturbances, SNF, PNP, severe headache, dizziness, “brain fog”, visual disturbances), and skin efflorescences. Local microvascular blood supply disturbances and the resultant ischemia are implicated in these adverse effects after the loss of RAAS-attenuating ACE2 activity. In this context, reversible cerebral vasoconstriction syndrome (RCVS) provoked by vasoactive agents, such as catecholamines or angiotensin II, becomes relevant as a cause of severe headache attacks. In the case of complex complaints, mixed forms involving neurovegetative components (autonomic neuropathy) must be considered.

The numerous side effects that occur far from the injection site clearly prove that the spikes or sites of their production are systemically distributed. Moreover, spike production is not limited to a few days.

The second indication of the class-specific side effects of spike-based vaccines is their repeatedly demonstrated spike/ACE2 interaction. For side effects based on this mechanism of action, it is proposed to use the collective term SPAS - spike induced disturbances (Spike ausgelöste Störungen in German) with micro/macrovascular, vasoconstrictive, vasculitic, and/or possible inflammatory/autoimmunological and blood-coagulation involvement.

Further adverse events may be caused by components of the finished product (different exogenous proteins and excipients). In principle, however, a class-specific side effect profile can be assumed.

Knowledge of the spike/ACE2 interaction and its effects

is essential not only for the acceptance and assessment of symptoms after vaccination, but also for diagnostic evaluation and therapeutic interventions. Regardless of a possible reduction in use, knowledge of the complete adverse event profile improves vaccine safety.

Limitations

This review/analysis has limitations resulting from the individual reporting system and non-validated collection method of both data sources. A structured, validated data collection system, as well as a monitoring system for the progression of adverse events, is lacking. The diagnostic clarification was quite insufficient.

To interpret the results, findings from an appropriate comparison population would be necessary, but these do not exist.

Further investigations are needed to clarify the systemic distribution of spikes, the duration of their production, and their dependence on local tissue factors, as well as studies clarifying the involvement of autoantibodies to ACE2, AT1, MasR, and angiotensin II, studies that distinguish between adverse reactions triggered by spike/ACE2 interactions and those triggered by exogenous proteins, or studies evaluating allergic reactions to each component of the vaccine. In addition, inflammatory and nerve transmission-disrupting spike effects should be studied in detail.

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