

Deaths Related to New-Onset Seizures After Vaccination

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ABSTRACT

Background: Adverse effects following vaccination are well-known. While most effects are mild and transient, some may be severe or even lethal. Particularly with regard to coronavirus disease 2019 (COVID-19) vaccinations, which were “fast-tracked,” it is incumbent upon the medical community to be diligent in identifying potential vaccine-associated adverse events so that physicians and patients can make truly informed decisions when considering the risks versus benefits of vaccination. **Objective:** To provide an in-depth discussion about post-vaccination seizures, particularly with regard to COVID-19 vaccinations. **Research Design:** Retrospective review of two cases where death was deemed to be the result of new-onset seizures; in each case, the seizures began shortly following vaccination. **Subjects:** In one case, death was certified by the primary care physician, without implicating the recent COVID-19 vaccination. In the other case, certified by the medical examiner, recent simultaneous vaccination with a COVID-19 vaccine and an influenza vaccine were considered to be contributory to death. **Measures:** The case specifics are presented for each case, including clinical work-up (both cases) and autopsy findings (one case). **Conclusions:** When attempting to determine whether or not a seizure-related death is due to a vaccine-induced new-onset seizure disorder, forensic pathologists need to rule-out other explanations for the seizures. Although a temporal association between seizures and vaccination is not sufficient, in and of itself, to prove causality, the temporal association, in combination with the absence of another explanation for seizures, and knowledge of similar cases in the medical literature, is sufficient to ascribe a causal role to the vaccination.

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INFORMATION

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INTRODUCTION

Vaccination against infectious diseases represents a major public health strategy in the United States and worldwide. Despite the reported public health benefits of large-scale vaccination programs, individual adverse reactions to vaccinations are well-known. Any serious and unbiased evaluation of vaccinations must involve a discussion of the risks versus the benefits of vaccinations, not only from a population-based public health standpoint but also from an individual, patient-centered, informed-consent viewpoint.

Here, we present two deaths that were attributed to new-onset seizures that developed following the administration of a coronavirus disease 2019 (COVID-19) messenger ribonucleic acid (mRNA) vaccination. One of the cases involved the simultaneous administration of an influenza vaccination, and the vaccinations were considered by the medical examiner (ME) to be a probable explanation for the seizures. In the other case, the decedent's primary care physician completed the death certificate without including the recent mRNA vaccination as a contributing cause. Pertinent details of the cases are presented, along with a discussion regarding vaccination-induced seizures, particularly as they relate to COVID-19 vaccinations, as well as the challenges that exist when attempting to determine whether or not a seizure (or other adverse outcome) can be linked to a vaccination.

METHODS

As part of the overall surveillance of unexpected deaths following the availability of COVID-19 vaccinations during the COVID-19 pandemic, the Medical Examiner's Office at Western Michigan University Homer Stryker MD School of Medicine decided to inquire about vaccination status when deaths were reported to the office. Depending on individual

circumstances, MEs made decisions regarding whether or not to further investigate a case, the extent of which could range from medical records review to performing an autopsy. Several cases were investigated during the years following COVID-19 vaccine availability in order to investigate the possibility that the deaths might be related to vaccination. Two in particular involved deaths that were deemed to be related to new-onset seizures that occurred shortly following COVID-19 vaccination. These cases were selected retrospectively and form the basis for this report.

RESULTS

Case 1

In the Spring of 2021, a 59-year-old female who had developed new-onset seizures following COVID-19 vaccination was found dead in her home. The case was reported to the ME. After consultation with her neurologist and primary care provider (PCP), the death certification was released from ME jurisdiction with the death certificate to be completed by the decedent's PCP.

The decedent was generally healthy except for excessive alcohol consumption, which did not, reportedly, disrupt her daily activities. She never had experienced seizure activity until after receiving her first Moderna COVID-19 vaccination. Five days after receiving her shot, she awoke on the floor, in a kneeling position, with her head on the floor, feeling as if she could not pick up her head. Those with her at the time of this event insisted that she go to the Emergency Department (ED), which she did, with subsequent discharge. Although there had been no preceding nausea or light-headedness, she attributed this episode to adhesive fumes from a construction project taking place in her home. She was not intoxicated with alcohol and had not been drinking prior to becoming

unresponsive. Twenty days later, she experienced a second episode, which was witnessed and was accompanied by facial twitching/contractions and a postictal state. She was again taken to the ED, where she was diagnosed with a new-onset seizure. Levetiracetam therapy was initiated, she was discharged from the ED, and she was referred to a neurologist for new-onset seizures. Six days later, she received her second dose of Moderna COVID-19 vaccination.

She remained seizure-free while on levetiracetam therapy, and subsequently underwent a comprehensive seizure work-up over the next 2 months, including 14-day cardiac patch-monitoring, a head computed tomography (CT) scan, a head magnetic resonance imaging, and an electroencephalogram, which were all negative regarding the identification of a cause for her new-onset seizures. At the time of her neurologic work-up, alcohol use was not considered by the neurologist as being a potential factor for her seizures. Importantly, her recent vaccinations were not reported by the patient to the ED or the neurologist, nor was she questioned about her vaccination history in any of her interactions with medical personnel during her seizure work-up.

The patient remained on levetiracetam therapy and continued to be seizure-free following her neurological work-up, but was found dead at home approximately 3 months after her initial seizure. ME's office discussions with the patient's PCP and neurologist revealed that neither believed that the seizures were related to COVID-19 vaccination. As such, death certification was remanded to the PCP, and an autopsy was not performed. The PCP completed the death certificate as follows: cause of death (COD): Chronic alcohol use complications (years) due to [sic] Seizure disorder (months); the manner of death (MOD) was considered natural. Despite this death certification, the case was referred to the Vaccine Adverse Event Reporting System (VAERS) by the ME's office.

Case 2

A 38-year-old male experienced a witnessed tonic-clonic seizure, became unresponsive, and died after failed resuscitation attempts by his wife, who was a nurse, and emergency medical services. The

decedent had experienced a witnessed first onset tonic-clonic seizure 20 days earlier, at which time he was evaluated in the ED, where a head CT scan was negative, laboratory tests were non-contributory, no official explanation for the seizure was identified, and he was discharged. He was awaiting an appointment for neurologic work-up. His wife reported that the decedent had experienced unusual sensations since he received his second Pfizer-BioNTech COVID-19 vaccine and a simultaneous influenza vaccine, 14 days before his first seizure. She also reported that he had demonstrated some memory deficits since that time. He had received his first Pfizer-BioNTech COVID-19 vaccination 6 months prior to his second dose, without any reported complications.

A full medicolegal autopsy was performed, which disclosed an obese male (Body Mass Index 43.7 kg/m²) with an enlarged heart (600 g) with associated cardiac myocyte hypertrophy, a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA nasal swab, but negative lung histology. A full neuropathology examination was performed by a Board-certified forensic neuropathologist, including an examination of the brain, the spinal cord, the dura mater, and the pituitary gland. No abnormalities were identified grossly or microscopically. Blood was sent for genetic arrhythmia/cardiomyopathy panel testing, which disclosed two variants of uncertain significance. Toxicology testing revealed cannabinoids within postmortem blood samples. Vitreous electrolytes were within normal limits. The COD was certified as follows: COD: seizure disorder; contributing causes: cardiomegaly; obesity; recent Pfizer-BioNTech COVID-19 vaccination and influenza vaccination. The MOD was ruled as natural. The case was referred to the VAERS.

DISCUSSION

COVID-19 Infection and Seizures

Before discussing post-vaccination seizures, it is important to note that seizures (and many other neurologic conditions) can also be part of the constellation of presentations occurring in persons infected with SARS-CoV-2, either as a direct result of the infection or as a complication of some other infection-induced

condition (1–5). In fact, new-onset seizures may be the first indication that someone has COVID-19 (2). COVID-19 infection is also reported to be capable of increasing the frequency of seizure activity in persons with epilepsy (PWE) (2). Another interesting finding reported by Mubarak et al is that many COVID-19 infection-related neurologic symptoms, including seizures, are significantly more common in COVID-19-infected patients who have been previously vaccinated (4). Seizures may also be associated with other infectious diseases. A case of suspected COVID-19 vaccine-related seizure occurred in a 15-year-old child 6–7 h after Covaxin vaccination in India, but it was determined that the seizure was related to Dengue fever, rather than the vaccine (6).

Adverse Reactions to COVID-19 Vaccinations

Adverse reactions to vaccinations are relatively common; however, most of these reactions are considered to be mild (7). Neurological adverse reactions may develop following vaccination, with many considered to be mild; however, serious neurological reactions may also occur (8). Potentially serious adverse reactions to vaccinations, including seizures, have been documented for decades,(9) well before the time of the implementation of the COVID-19 vaccines. Physicians have also known for decades that, when suggesting any therapy, including vaccination, informed consent is essential so that patients can understand the risks versus the benefits of a proposed therapy (9). Consequently, and especially in light of the fact that the COVID-19 vaccinations were “fast-tracked” for widespread implementation (without multi-year clinical trials), it is imperative that any potentially serious complications occurring following vaccination be fully investigated (10). As Nunez et al state, “Given the relatively small number of patients included in vaccine trials, post-approval epidemiological surveillance is crucial to detect infrequent vaccine-related adverse events” (11). As such, case reports such as presented herein, can be valuable additions to the medical literature regarding vaccination-related adverse events. The ensuing discussion will focus on neurological adverse events, especially seizures, as they relate to the COVID-19 vaccines.

The temporal association of a potential adverse reaction and vaccine administration does not prove a cause-and-effect relationship. Because of the background incidence rates of various neurological conditions in the general population, and the very large numbers of people receiving the COVID vaccines, from a statistical standpoint, some of these neurological conditions will appear in the post-vaccination period by chance (12). Therefore, establishing a causal link is difficult (12). Even now, several years after the advent of the COVID-19 vaccines, it can be difficult to prove a cause-and-effect relationship, since there is a shortage of comprehensive, prospective studies (3). However, the close temporal relationship between vaccination and symptoms, the biological plausibility explaining the link, and an extensive diagnostic work-up to exclude other potential explanations/causes of the symptoms are sufficient, according to the World Health Organization’s criteria for causality assessment, to link an adverse event following vaccination on an individual level (12). The Brighton Collaborative Criteria for Adverse Events Following Immunization (AEFI) was initiated in 2000 in order to evaluate possible adverse events, such as anaphylaxis, following vaccination, (13) with more specific tracking of adverse events specifically involving viral vector vaccines in 2008 (14). As of 2020, the newly-named “Benefit-Risk Assessment of Vaccines by TechnoOgy” is available via the Brighton Collaboration in order to evaluate the safety of vaccines that utilize a variety of methodologies, including viral vectors, protein subunits, nucleic acids, inactivated viruses, and live-attenuated viruses (14). Templates for the collection of key information for benefit-risk assessment have been published for each of the methodologies (15–19). In general terms, there are at least two criteria that may suggest that an adverse event may be related to a vaccine: 1) the presence of a clearly defined time window of increased risk to establish the temporal relationship of the event to the vaccine; 2) the availability of evidence in the literature to support a consistent relationship to the vaccine (20,21). More specifically, when assessing the potential causality of an adverse event in relation to a vaccine at the individual patient level, the World Health

Organization recommends taking into consideration the following: 1) Temporal relationship—the vaccination must precede the event; 2) Presence or absence of definitive proof that the vaccine caused the event; 3) Population-based evidence for causality; 4) Biological plausibility; 5) Consideration of alternative explanations; 6) Prior evidence that the vaccine in question could cause a similar event (20). If these criteria are met, it is reasonable to opine that an individual patient’s adverse event was likely due to a vaccine (12). Despite this, proving a causal link on a population level requires large, long-term epidemiologic studies and cannot be based on individual case reports alone (12).

As of 2023, there were at least 14 different anti-SARS-CoV-2 vaccines available worldwide, including several within the following general categories: mRNA, viral vector, and protein subunit (22). Despite the lack of comprehensive prospective studies examining adverse events following COVID-19 vaccine administration, there is mounting evidence which suggests that, although rare, adverse reactions of many types can and do occur in relation to inoculation with these vaccines. In a systemic review of the available literature as of mid-2022 regarding adverse events associated with mRNA-based COVID vaccines, the authors reported that serious and severe adverse events were rare and that a causal relationship had not been established in most cases (23). The most important adverse events were myocarditis/pericarditis in younger vaccine recipients, thrombocytopenia, neurological effects including seizures and orofacial disorders, skin reactions, and allergic hypersensitivities (23). In a different 2022 study, Yan et al reviewed serious adverse reactions associated with COVID-19 vaccines reported to the VAERS; the serious adverse reactions included thromboembolism, hemorrhage, thrombocytopenia, cardiac arrhythmia, hypertension, hepatotoxicity, cardiac failure, acute renal impairment, and seizures (24).

Neurologic Adverse Reactions to COVID-19 Vaccinations

Specifically with regard to the overall theme of neurologic adverse reactions to COVID-19 vaccination,

numerous studies have been published within the medical literature over the past 3 years (1,3,21,22,25–29). **Table 1** provides an overview of the many and various neurologic side effects that have been reported following COVID-19 vaccination. Many of the most common neurologic adverse events are considered to be transient and mild; multiple reviews (3,26,27) provide a listing of these neurologic conditions and variably include several of the following: headache (of a variety of subtypes), sensory symptoms (burning, paraesthesia, hyperaesthesia, hypoaesthesia; numbness; hyper-responsiveness to stimuli; neuralgia, neuropathy), spasms, weakness, anosmia (loss of the sense of smell), dysosmia (distorted sense of smell), ageusia (loss of the sense of taste), dysgeusia (distorted sense of taste), myalgia, dizziness, balance disorders, and sleep disturbances (hypersomnia, hyposomnia). Other rare, but perhaps more worrisome, side effects include tremor, diplopia, tinnitus, dysphonia, delirium, and syncope (3). Neurological side effects can occur with any COVID-19 vaccine type; they are diverse in their presentation and are usually mild, but some are very serious or even fatal (22). Severe neurological adverse reactions to COVID-19 vaccinations have been reported by numerous authors (1,3,22,25–29) to variably include the following: central nervous system (CNS): vascular events (central venous sinus thrombosis [CVST], ischemic stroke, intracerebral hemorrhage, transient ischemic attacks, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, subarachnoid hemorrhage), metabolic disorders (new-onset seizures, status epilepticus (SE), neuromuscular malignant syndrome), inflammatory conditions (acute disseminated encephalomyelitis, encephalitis, meningitis, Susac syndrome), and functional (neuropsychiatric) disorders; spinal cord: acute transverse myelitis, longitudinally extensive transverse myelitis, new-onset multiple sclerosis, neuromyelitis optica spectrum disorders; cranial nerves: optic neuritis, cranial nerve palsies (Bell’s palsy, Abducens nerve palsy, and Tolosa-Hunt syndrome); peripheral nerves: Guillain-Barre syndrome, Chronic demyelinating polyneuropathy, Miller Fisher syndrome, Parsonage–Turner syndrome, myasthenia gravis, herpes zoster reactivation, small fiber neuropathy; muscular—myositis, dermatomyositis, rhabdomyolysis, paresis.

Table 1. Neurologic Adverse Reactions Reported With COVID-19 Vaccinations.

Category	Examples
Common mild transient neurologic effects	Headache Sensory symptoms (burning, paraesthesia, hyperaesthesia, hypoaesthesia, numbness, neuralgia, neuropathy, hypersensitive to stimuli) Spasms Weakness Anosmia or dysosmia Ageusia or dysgeusia Myalgia Dizziness Balance disorders Sleep disorders (hypersomnia, hyposomnia)
Rare potentially worrisome neurologic effects	Tremor Diplopia Tinnitus Dysphonia Delirium Syncope
CNS vascular events	CVST Ischemic stroke Intracerebral hemorrhage TIA Posterior reversible encephalopathy syndrome Reversible cerebral vasoconstriction syndrome Subarachnoid hemorrhage
CNS metabolic disorders	New-onset seizures Increased frequency/severity of seizures SE NMS
CNS inflammatory conditions	ADEM Encephalitis Meningitis Susac syndrome
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Functional (neuropsychiatric) disorders	
Spinal cord disorders	Acute transverse myelitis LETM New-onset MS NMOSD
Cranial nerve disorders	Optic neuritis Cranial nerve palsies (Bell's palsy, abducens nerve palsy, Tolosa-Hunt syndrome)
PNS disorders	GBS CDP Miller Fisher syndrome Personage-Turner syndrome MG Herpes zoster reactivation Small fiber neuropathy
Muscular disorders	Myositis Dermatomyositis Rhabdomyolysis Paresis

Source: Aliasin (1); Mohseni Afshar (3); Koh (21); Finsterer (22); Koh (25); Garg (26); Dutta (27); Assiri (28); Devaraj (29).

Abbreviations: CVST, central venous sinus thrombosis; CNS, central nervous system; TIA, Transient ischemic attacks; SE, status epilepticus; NMS, neuromuscular malignant syndrome; ADEM, acute disseminated encephalomyelitis; LETM, longitudinally extensive transverse myelitis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; GBS, Guillain-Barre syndrome; CDP, chronic demyelinating polyneuropathy; PNS, peripheral nervous system; MG, myasthenia gravis.

Seizures Following COVID-19 Vaccination

Seizures following COVID-19 vaccinations can occur in two general patient populations: 1) In those who have never experienced a seizure previously, as occurred in the two cases presented in this report. 2) In those who have pre-existing seizures, so-called “persons with epilepsy” or PWE. A 2021 study from Singapore examined neurologic events following COVID-19 vaccination in seven public hospitals during the first 4 months of 2021 (25). Of 33 patients who presented with seizures, 22 experienced the seizure within 2 weeks of vaccination; of these, 4 were new-onset seizures, while the remaining 18 had a previous diagnosis of epilepsy or some other cause for the seizures (25). Twenty-two of the 33 patients experienced a seizure after the first dose of the vaccine, while the remaining 11 had a seizure after the second dose (25). Latency from vaccination to seizure in the 33 patients ranged from 0 to 38 days (25). A retrospective, observational, hospital-based study from Spain, encompassing January through December of 2021, reported that 26 PWE experienced an increased frequency of seizures in the first month after vaccination, while 15 patients presented with new-onset seizures within 1-month of having received a vaccination (30). A Mexican study evaluated the incidence of seizures among recipients of COVID-19 vaccines from December 24, 2020 to October 29, 2021, based on a review of Mexico’s AEFI system (11). A total of 53 patients reported seizures following vaccination to the AEFI, 31 of which were new-onset seizures (11). During the trial period, Mexico had 7 approved vaccines, and the highest incidence of seizures occurred in the Moderna vaccine, followed by Pfizer and CanSino (11).

New-onset seizures following COVID-19 vaccination. If a person who has never experienced previous seizure activity experiences a seizure, the condition can be referred to as a “new-onset” seizure. When presented with such a patient, it is incumbent on the medical team to attempt to determine the cause of the seizure activity. When the new-onset seizure occurs following a vaccination, it is reasonable to suspect that the vaccination may have had something to do with initiating the seizure activity. The temporal association between

vaccination and seizure onset plays a role in how confident one can be in linking the vaccination to the seizure; however, as discussed previously, temporal association is insufficient in and of itself to confirm causation. As will become evident in the following paragraphs, unlike classical “allergic reactions,” post-vaccination seizures do not need to occur within a relatively short time frame (hours to days) in order to make a possible connection between the vaccine and seizure. Ultimately, on an individual case basis, if the new-onset seizure occurs following a vaccine, even if it occurs weeks after the vaccination, then the vaccine should be considered as a possible cause for the seizure. If no other explanation for the seizure activity can be identified, then, for that individual instance, it is reasonable to conclude that the vaccine was the cause of the seizure. This will be discussed further below.

New-onset seizures following COVID-19 vaccinations have been reported numerous times in the literature (1,3,12,22,28,29,31–46). Many of these studies represent simple case reports or case series, so population-based statistical conclusions cannot be drawn from such cases alone; however, when evaluating these cases on an individual basis, most provide compelling evidence that the seizures were likely related to vaccination. According to one very comprehensive review of the neurologic side effects of COVID-19 vaccines, seizure (epilepsy) is considered a “repeatedly reported” side effect, compared to other side effects that are either “common” or “rare” (22). Post-vaccine seizures following COVID-19 vaccination may occur as febrile seizures, in association with other neurological symptoms and/or associated structural defects, in relation to psychological stressors, or as de novo unexplained seizures.

Febrile seizures are seizures that occur in the setting of a febrile illness. Vaccinations are the second-leading cause of febrile seizures and are defined as seizures occurring up to 72 h following a vaccination (1,47). Although the exact mechanism of febrile seizures is not fully understood, one possible mechanism is related to specific ion channel alterations and increased neuronal firing triggered by certain cytokines, with a possible role of genetic predispositions in the

gamma-aminobutyric acid type A (GABA-A) receptor and sodium channels, thus decreasing the seizure threshold in relation to cytokine levels, especially interleukin-1 (1,47,48). Febrile seizures following COVID-19 vaccination are relatively rare (1). The possible occurrence of febrile seizures following COVID-19 vaccination is supported by the fact that a small number of patients with Dravet syndrome (an epileptic encephalopathy that occurs with early-onset seizures followed by afebrile seizures later in life) reported an increase in seizure frequency after their first dose of COVID-19 vaccine (1,31).

In addition to post-vaccination febrile seizures, new-onset seizure activity has been reported following COVID-19 vaccination in association with vaccine-induced encephalitis/encephalopathy, (1,3,12,22,32,34–38) CVST,(1,3,22,28,33) and stroke (1,22,28). In some reported cases, a definite underlying/intermediary neurological condition was not diagnosed but may have been present based on pre-seizure symptoms, such as in the case of a woman who developed SE 8 days after receiving her second Pfizer-BioNTech COVID-19 vaccine, with fever, skin rash, and headache occurring after the vaccination but before SE (39). Specific structural/anatomic lesions of the CNS, such as strokes and CVST, may result in seizure activity related to hypoxic or other insults to the brain (22). Vaccine-induced encephalopathy/encephalitis, as well as certain other neurologic sequelae, might be related to cytokines elaborated by the vaccine (32). It has been suggested that the interplay of spike proteins (via COVID-19 infection or elaboration by vaccination), angiotensin-converting enzyme 2 receptors, and transmembrane serine protease 2, may explain why certain CNS cells are at risk for untoward effects of infection or vaccination (1). The elaboration of various autoantibodies following COVID-19 vaccination has also been suggested as a possible explanation for certain cases of post-vaccination autoimmune encephalitis, (49) with possible associated seizure activity. More specifically, anti-*N*-methyl-D-aspartate receptor antibody-related encephalitis has been reported following Pfizer-BioNTech mRNA COVID-19 vaccination (49,50). Another example of post-vaccine autoimmune encephalitis associated with new-onset seizures involved a 16-year-old who presented with multiple tonic-clonic

seizures 1 week following Pfizer-BioNTech vaccination (12). A work-up for another cause of the seizures was negative; however, new-onset insulin-dependent diabetes mellitus was diagnosed, and it was postulated that vaccine-induced anti-glutamic acid decarboxylase antibodies may have played a role in both the diabetes and encephalitis, (12) since glutamic acid decarboxylase is an intracellular enzyme that converts glutamate to GABA, (51) and GABA is an inhibitory neurotransmitter in the CNS and is associated with paracrine signaling in pancreatic islet cells (52). Several autoantibodies that may play a role in thrombus formation (or other neurologic sequelae following vaccination) have been reported in relation to COVID-19 vaccinations, including glycoprotein-specific platelet autoantibodies, anti-GPIIb-alpha autoantibodies, and antineutrophil cytoplasmic autoantibodies (49).

In other post-COVID-19 vaccine new onset-seizure cases, various metabolic or physiologic derangements have been identified, with or without additional symptoms/conditions. For example, a case of the syndrome of inappropriate antidiuretic hormone (hyponatremia) and SE occurred in an 83-year-old man who presented with headache and weakness 3 days after a Pfizer-BioNTech vaccination (40). In a different case, a 48-year-old woman presented to the ED 1 day after her second Pfizer COVID-19 vaccination, with confusion, severe headaches, depressed consciousness, and possible seizure activity, as well as severe hyponatremia and cerebral edema (41). Another condition that has been reported after COVID-19 vaccination that may be associated with seizures is “reversible cerebral vasoconstriction syndrome” (53). de Almeida et al report a case of new-onset tonic-clonic seizures 5 h after receiving the Johnson & Johnson vaccine, with no identifiable mechanisms; however the 32-year-old patient had a history of cerebral hypoxia at age 13 years due to drug use, with residual left-sided spasticity, but never any seizure activity, thus suggesting that pre-existing brain lesions might increase one’s risk of post-vaccination seizures (42). It has been suggested that seizures might be induced by vaccine-activation of the immune system, or via vaccine-induced electrolyte imbalances (42). One possible explanation is that vaccine-induced spike proteins stimulate an

exaggerated inflammatory condition along with hyperthermia, which induces glial cell activation and increases blood-brain permeability, thus allowing peripheral blood cells and albumin to more freely pass into the CNS; this leads to a disruption of the CNS osmotic balance and allows for increased circulating cytokines within the CNS, resulting in seizure activity (28).

In rare instances, post-vaccination new-onset seizures are deemed to result from psychological stressors (1,43,44). Such psychogenic seizures are reportedly related to the fear of vaccination, and have been classified as an “immunization stress-related response.” (1,43,44)

The final subtype of post-COVID-19 vaccine new-onset seizures is characterized by occurrences de novo, without recognized associated underlying mechanisms or stressors (3,12,28,29,45,46). The two cases reported in this report fall into this category. The incidence of new-onset de novo seizures occurring within 4 weeks of receiving any COVID-19 vaccine, as reported to the VAERS, was determined to be 3.19 seizures per 100,000 persons per year for U.S.-approved COVID vaccines, with similar rates for the Pfizer and Moderna vaccines and a slightly lower rate for the Janssen vaccine (46). For comparison, the incidence of new-onset seizures per 100,000 persons per year for influenza vaccines was only 0.09 (46). Also for comparison, the incidence rates per 100,000 people per year for headaches with COVID-19 vaccinations was 93.7, while for influenza vaccination it was just over 1.0 (46). Mechanisms involved in de novo new-onset seizure activity following COVID-19 vaccination likely mirror those described above, in relation to electrolyte imbalance and/or cytokine/inflammatory mechanisms. Some have suggested “transient CVST” as a cause, with spontaneous resolution of the CVST by auto-anticoagulation (42).

Seizures in PWE following COVID-19 vaccination. Although neither of the persons described in this report had a prior history of seizures, for completeness’ sake, a brief discussion regarding post-vaccination seizures in PWE will be provided. In the PWE population, “breakthrough seizures” can occur

following COVID-19 vaccination in patients whose seizure activity has been previously well-controlled (3,28,31,54–58). Although one study concludes that the frequency of seizures in PWE (excluding those with immunologically-mediated epilepsy) after receiving non-mRNA COVID-19 vaccinations is not significantly increased, (55) several other studies indicate an increased frequency in PWE among all vaccine recipients (56,57) and among those who received an mRNA vaccine (58). Nonaka et al reported that approximately 6% of PWE exhibited worsening of seizures after mRNA vaccination, usually within 48 h (58). Those most susceptible were PWE with focal impaired awareness seizures, high baseline seizure frequency, and drug-resistant epilepsy (58). An Australian study reported that 2.5% of PWE participating in an epilepsy clinic study reported an exacerbation of seizures after the first COVID-19 dose (56). A meta-analysis showed a 5% increased seizure frequency following COVID-19 vaccination in PWE (57).

Studies suggesting that vaccines do not cause seizures. Several often-cited studies within the literature suggest or otherwise strongly imply that COVID-19 vaccines do not impart an associated increased risk for seizures, including seizures in general (11,25,30,59,60), or seizures in PWE (54). The findings, conclusions, and recommendations of such studies may explain why many healthcare professionals and public health officials claim that COVID-19 vaccinations are not associated with seizures. In light of the ongoing controversy surrounding the potential adverse reactions related to COVID-19 vaccines, it is appropriate to take a closer look at each of these studies.

A study reviewing the neurological events after COVID-19 vaccines as reported to the VAERS suggested that only the Janssen vaccine was associated with an increased risk of seizures (59). This study reported the incidence of various neurologic adverse events and also calculated observed-to-expected (O:E) ratios for these neurological events occurring after COVID-19 vaccination using only data voluntarily reported to VAERS (59). Thus, the numerator for the incidence of events was the number of cases reported to the VAERS, while the denominator was the total number of vaccines administered (59). Since not all

adverse events are reported to VAERS, the incidence numbers are almost certainly underestimated in this study. The study also used questionable statistical data for determining the expected “background” neurologic events. For example, the results suggested that only the Janssen vaccine was reported to have an O:E ratio greater than 1.0 for seizures (O:E of 1.87), while the O:E for the Pfizer and Moderna vaccines was less than 1.0, at 0.633 and 0.59 respectively (59). If these numbers are correct, the implication is that the mRNA vaccines must apparently be protective against developing seizures. It is interesting to note that, in addition to seizures, the report also provided O:E ratios for numerous other neurologic adverse events, including central venous thrombosis, ischemic stroke, intracerebral hemorrhage, encephalitis, Guillain-Barre syndrome, and acute disseminated encephalomyelitis, to name a few (59). With rare exceptions, the mRNA vaccinations had O:E ratios of less than 1.0, sometimes quite impressively less than 1.0 (59). If these numbers are to be believed, then one could argue that the mRNA vaccines are protective against a number of potential adverse neurologic events, not just seizures. Since numerous other studies indicate otherwise, one has to question the statistical methodologies employed in this study. Even using the background rates of various conditions from pre-pandemic conditions may be fraught with error. As stated by Phillips et al, “Accurate and consistent background rates are a critical component in the conduct of reliable observed versus expected analyses. However, rates may vary across different populations, geographical regions, and over time, ... and may relate to underlying differences in populations, care-seeking behavior, access to care, diagnostic and coding practices” (61).

A study from Israel concluded that mass vaccination with the Pfizer-BioNTech mRNA vaccine is not associated with increased seizure frequency, either as new-onset seizures or as seizures occurring in PWE (60). This retrospective study was based on a single academic tertiary hospital’s ED visits for seizures, with a comparison of these numbers to numbers from pre-COVID years and the pre-vaccination COVID-19 year of 2020; the numbers were adjusted for “the total number of ED visits at the same time” (60). The authors made the “adjustment” (correction) because there were fewer ED visits for all causes

during the COVID years (60). Total annual ED visits in the years 2017–2019 were between 72,000 and 73,000, while the total number in 2020 was just under 61,000 and just under 70,000 in 2021 (60). Meaningful comparison of the numbers in the pre- and post-COVID years is potentially fraught with error due to the changes in care-seeking behavior that accompanied the pandemic. Regarding the comparison of the pre-vaccination COVID-19 year (2020) and the post-vaccination year (2021), the absolute number of patients presenting to the ED with seizures actually increased (313 in 2020; 339 in 2021) (60). Interestingly, the study also reported the number of patients presenting to the ED for seizures that were discharged versus the number of patients who were admitted to the hospital, but the vaccination status of these two groups was only known for the group that was admitted to the hospital; the data related to vaccination status of those persons who were not admitted to the hospital was not attainable “due to bureaucratic and patient privacy constraints” (60). This is especially troubling. The study declares that “we have shown that there was no increase in the number of visits to the ED due to seizures following a nationwide vaccination operation” (60). While the statistics as reported may demonstrate this to be true, one reasonable implication of such a statement is that the vaccine-status of all persons presenting to the ED for seizures was known; however, this was not the case. While the study does report that “the fraction of new-onset seizures among hospitalized patients was not increased in vaccinated patients compared to unvaccinated patients,” a similar comparison in persons discharged from the ED could not be made because the vaccination status for these individuals was not known (60). This was not an insignificant number. Over half (nearly 52%) of all patients presenting to the ED for seizures in 2020 and 2021 were discharged (60). As exemplified by the two cases presented in this report, it is not unusual for patients experiencing a new-onset seizure to be discharged after initial evaluation in the ED. The lack of information regarding the vaccination status of the discharged patient population represents a major drawback of this study.

A concluding remark in the previously-cited hospital-based Spanish observational retrospective report by

Martinez-Fernandez et al (see above - first paragraph under Seizures Following COVID-19 Vaccination) states, “SARS-CoV-2 vaccines appear to have little impact on the generation or decompensation of seizures” (30). This statement seems to imply that the vaccines have *no* impact on seizures, and yet, that is *not* what it says. Instead, it says “little impact.” The authors report that over 6% of PWE reported an increase in seizure frequency, and reported 15 new-onset seizures following vaccination (30). The study is further limited in that it is only hospital-based, and it only includes seizures occurring within 1 month of vaccination (30).

The previously-cited 2022 nationwide Mexican retrospective descriptive study by Nunez et al, which evaluated the incidence of seizures among recipients of COVID-19 vaccines, concludes that “we found that seizures following SARS-CoV-2 vaccination are exceedingly rare events” (11). This study was based on the AEFI system in Mexico, a system of reporting that is presumably similar to the VAERS system in the United States, with both being considered “passive” epidemiological surveillance systems (11). Local health authorities, private or public hospitals, and physicians submit reports of possible adverse events following vaccination to the AEFI (11). As such, any statistical conclusions that are reported have the potential for underestimating true incidence. As with the report by Frontera et al using VAERS data (59), cited above, the statistical analyses in this study are also questionable, since the numerator is based only on AEFI numbers, while the denominator was the total number of vaccines administered during the study period (11). The authors of this study recognize this as a limitation of the study and additionally suggest that probably only the most “overt” of seizures are reported to the AEFI, with other seizure types probably being unrecognized, confused with other entities, such as syncope, and/or likely to be under-reported (11). Indeed, the authors also provide an extremely important statement regarding why it is vital that we continue to pay attention to potential adverse events related to COVID-19 vaccinations: “Given the relatively small number of patients included in vaccine trials, post-approval epidemiological surveillance is crucial to detect infrequent vaccine-related adverse events” (11).

The previously-cited 2021 Singapore study of neurologic events following COVID-19 vaccination by

Koh et al, makes the following statements: “Our observational study does not establish causality of the described disorders to vaccines.”—“...we observed no obvious signal of serious neurological morbidity associated with mRNA vaccination.”—“The benefits of COVID-19 vaccination outweigh concerns over neurological adverse events” (25). This represents another example of attempting to apply population-based statistical analyses to recommendations for individual patients. Regarding the statistical analyses in this report, it should be noted that, for calculating the incidence of neurologic disorders, including seizures, following COVID-19 vaccination, the authors collected data from seven public hospitals in Singapore (the numerator), but then apparently used the total number of vaccinations administered in the entirety of Singapore as the denominator (25). According to the Singapore Ministry of Health website, in 2021, there were 19 “acute hospitals,” of which 10 were public, 1 was not-for-profit, and 8 were private, as well as 9 “community hospitals,” of which 5 were public and 4 were not-for-profit (62). Certainly, the seven public hospitals that were included in the study were not the only Singapore hospitals to evaluate post-vaccine patients for potential adverse neurological events. Another potentially limiting factor regarding the statistics in this study was the fact that it only included persons who were hospitalized as a result of their adverse reactions (25). In addition, specifically with regard to post-vaccination seizures, Koh et al apparently only included persons who experienced this potential side effect if the seizures occurred within the first 2 weeks following vaccination (25). Furthermore, if one reads through the data provided in this report, one finds that the authors actually consider a small number (four) of post-vaccine seizures as “probable” vaccine-related seizures, and several more cases (eighteen) as “possible” vaccine-related seizures (25). In a report from many of the same authors, regarding the recurrence of neurological events following re-immunization, Koh et al report a rate of only 2%, but that involves the entire constellation of neurologic adverse events (21). In evaluating the numbers, it appears that, specifically for seizures, of 181 patients who experienced an adverse event and elected to undergo re-immunization, 17 experienced seizures as the adverse event following

initial vaccination; of those 17, 3 experienced another seizure following re-immunization (21). This 17.6% recurrence rate (higher than 1 in 6) for seizures was not highlighted by the authors; however, they provide the following conclusion: “A prior neurological event should not necessarily preclude reimmunization and the decision to proceed with reimmunization should consider the overwhelming benefits conferred by vaccination toward ending this pandemic” (21).

Regarding COVID-19 vaccination in PWE, it is worth mentioning that, despite the evidence to the contrary (as briefly described previously), the “general consensus” espoused by some within the medical community continues to imply or otherwise explicitly state that there are no harmful side effects. Two examples will be provided specifically in relation to PWE. Sin et al report a 56-year-old patient with well-controlled secondary epilepsy (resulting from a cerebrovascular accident 9 years previously and a traumatic subarachnoid hemorrhage 3 years previously) who developed SE the day after receiving his first dose of an mRNA COVID-19 vaccine (54). After 90 min, medical intervention eventually brought him out of SE, and he remained in the intensive care unit for 7 days before being discharged (54). Despite this rather severe reaction to the vaccine, the authors conclude that “The benefits of COVID-19 vaccine protection far outweigh the risks of an allergic reaction and/or other side effects of the vaccine” and “there is currently no specific treatment against COVID-19. Therefore, the benefits of COVID-19 vaccine protection outweigh the risks” (54). While these statements may be true from a population-based public health standpoint, it is difficult to comprehend how the authors can apply such statements to the individual described in the case report after he endured 90 min of SE and a 7-day intensive care unit stay. The authors can perhaps be given some grace in reference to their somewhat absolute and idealistic statements, since their report was published relatively early in the post-vaccination era (2021), when we were still within the midst of the worldwide pandemic. However, the next example involves a current-day instance of minimizing the potential side effects of COVID-19 vaccinations.

The “Epilepsy Foundation” is a very well-respected organization whose mission is “to lead the fight to

overcome the challenges of living with epilepsy and to accelerate therapies to stop seizures, find cures, and save lives” (63). While the foundation does not officially offer medical advice, it does provide much valuable information for PWE and care-providers. On the Epilepsy Foundation website, there is a question/answer section regarding COVID-19 and COVID-19 vaccinations. One of these questions is, “Are those with epilepsy at higher risk of side effects?” The response is as follows, “There is no evidence that persons with epilepsy are at higher risk of side effects after vaccination.” The very next sentences state, “As with any vaccine, some persons may develop a fever which could lower their seizure threshold for the short term, and rarely could result in a break-through seizure. There is no evidence that this vaccination results in worsening of the epilepsy, or brain injury” (64). The semantics involved with these statements allow for them to be potentially misinterpreted. In the first statement, there is no qualifier regarding whom the PWE are being compared to in terms of their risk for side effects, and there is no presentation of which side effects are being compared. Side effects from the vaccines are quite common, but most are considered to be mild. It is almost certain to be true that injection site pain, or many other mild side effects, are more common than the 2.5–6% of PWE who experience worsening or increased frequency of their seizures. The last sentence explicitly states that the vaccinations will not result in the worsening of epilepsy, and yet the available data as presented above clearly indicates that for a small percentage of PWE, this is not true. Most within the medical community would consider increased seizure frequency as “worsening of the epilepsy.” This discussion is not meant to denigrate an outstanding organization, but is offered instead to encourage them and others like them to be as truthful and unbiased as possible when presenting information to those they serve.

To conclude this section, it may be instructional to note the recommendation of a panel of experts who reviewed cases in an observational study of potential adverse reactions to COVID-19 vaccines (including seizures) among employees and healthcare providers within a large healthcare system with over 40,000 employees; the study was undertaken as a quality-

improvement initiative of the healthcare system (65). Regarding the possible role of a COVID-19 vaccine in inducing seizures, the panel of experts recommended against a second dose of vaccine in persons who experienced a seizure following their initial dose (65). This study and its recommendations provide insight into “real-life” scenarios involving potential adverse reactions to the COVID-19 vaccines. The study not only involved a relatively large cohort of cases, but the experts were presumably not simply reviewing case numbers from some “distant” data mill; they were reviewing de-identified cases of colleagues, coworkers, and individuals whose adverse reactions might impact the overall wellbeing of their own community and healthcare system. As such, it is interesting to note that the overall recommendation was one of erring on the side of caution. Despite any population data that suggests that the vaccines might not statistically increase the chance of new-onset seizures, these experts chose to recommend, on an individual, case-by-case basis, an abundance of caution, with avoidance of subsequent vaccination in order to avoid vaccine-associated seizures (65).

Post-influenza vaccination seizures and seizures following simultaneous vaccination. In one of the cases presented, seizure activity occurred following the simultaneous vaccination with a COVID-19 vaccine and an influenza vaccine. Seizures have been reported following influenza vaccines (1,8,66). Seizure frequency following influenza vaccine, as per VAERS data, has been estimated to be 0.090 per 100,000 per year, compared to 3.191 per 100,000 per year following COVID-19 vaccination (46). Regarding simultaneous vaccinations involving COVID-19 vaccinations, Kenigsberg et al reported statistically significant adjusted rate ratios for “convulsions/seizures” following the first dose of the vaccine (67). This provides more evidence to support the conclusion in Case 2 that the new-onset seizure disorder, and subsequent death, were related to vaccination.

Forensic Pathology Investigation of Seizure-Related Deaths

It is well-known within the forensic pathology community that death may be the result of seizure activity. Like a variety of other causes of death, sudden

unexpected death in epilepsy is a diagnosis of exclusion (68). In the typical case, an individual with a known history of epilepsy experiences a sudden, unexpected death without an identifiable toxicological or anatomical COD (68). Historical context is key in such cases, and medicolegal death investigators should always attempt to ascertain the source/etiology of a seizure disorder when a person with such a disorder dies suddenly and unexpectedly. At autopsy, for a death to be considered to be due solely to a seizure disorder, the autopsy has to exclude all other possible explanations for death. While the sudden unexpected death in epilepsy definition is important, it is also important to note that sudden death related to seizures can also occur in other persons with “epilepsy,” including in those with a recognizable lesion or past trauma that is considered to be the source of the seizure disorder. Regarding post-vaccination seizures, it should be apparent based on the preceding discussion that post-vaccination seizures can and do occur, not only in relation to COVID-19 vaccinations but also with other vaccinations. Despite the controversies regarding population-based, statistical incidence/frequency reports of post-COVID-19 vaccination seizures, it should also be apparent that, on an individual, case-by-case basis, there might be sufficient evidence to ascertain a probable link between a vaccine and a seizure, and even a subsequent death that is attributable to the seizure. As alluded to earlier, if a new-onset seizure occurs after vaccination, within hours to weeks, and there is no other explanation for the seizure (negative clinical neurologic work-up), it is reasonable to conclude that the seizure was caused by the vaccination. If death occurs and the subsequent investigation excludes all other explanations for death other than the seizure disorder, it is also reasonable to consider the death to be the result of the seizure disorder. If no other explanation for the seizure is identified (negative neuropathologic examination), then it is reasonable to conclude that the vaccination was the likely cause of the seizure.

In Case 1 of this report, a previously healthy 59-year-old female, with a history of “excessive” alcohol use, developed post-COVID-19 vaccination seizures and was found dead at home without any other explanation for death. She had recently undergone a complete neurologic work-up for seizures

which was negative. Both the PCP and neurologist were unaware of the history of recent COVID-19 vaccination in this case, but even after receiving this information, did not consider the vaccination as a reasonable explanation for the seizure disorder. Instead, the death certificate completed by the PCP listed “chronic alcohol use” as the explanation for the seizure disorder, although this was not ever considered during her seizure work-up, either by the PCP or the neurology team. The ME office relinquished jurisdiction in this case, in part, because the PCP had indicated that they would be willing to complete the death certificate, and also because there was no trauma or foul play suspected during the initial investigation. The case serves, perhaps, as an example of a situation where healthcare professionals might have been unwittingly influenced by errant information regarding vaccine-associated seizures.

In Case 2 of this report, a 38-year-old man experienced a witnessed and medically documented tonic-clonic seizure 2 weeks after receiving his second COVID-19 vaccine, along with a simultaneously administered influenza vaccine. Initial ED work-up, including a CT scan and laboratory testing, was negative, and he was awaiting a full neurologic work-up when he experienced another witnessed seizure and died. Full medicolegal autopsy, including complete autopsy, toxicological analysis, and neuropathological examination, revealed no explanation for the seizure, but cardiomegaly and obesity were documented. In this case, the temporal association between the vaccines and the new-onset seizures, the lack of another satisfactory explanation for seizure activity, the fact that the decedent experienced sudden death during a witnessed seizure, the lack of another, more adequate explanation for death, and the available medical and scientific literature which proposes a link between the vaccinations and seizures, all led the forensic pathologist to the conclusion that death was the result of a seizure, with contributing factors of cardiomegaly, obesity, and recent COVID-19 and influenza vaccination. The MOD was natural.

Depending on the circumstances of the lethal seizure disorder, the MOD may be considered something other than natural. For example, if a man sustains a

gunshot wound of the head at the hands of another individual and survives with a post-traumatic seizure disorder, and then dies months or years later as a result of the seizure disorder, the MOD is appropriately considered a homicide (69). When therapies, including vaccinations, are considered to be contributory to death, several options exist for MOD certification, including natural, accidental, and “therapeutic complication,” in jurisdictions where the latter is available as a choice for MOD. How one certifies the MOD in deaths related to medical therapy depends, to an extent, on how that person was trained, office convention, pathologist convention, the type, mechanism, or timing of therapeutic complication involved, or even on the varying specifics of a particular case. According to the National Association of Medical Examiners “Manner of Death Guidelines,” deaths due to “reasonably foreseeable complications of an accepted therapy for natural disease” may be classified as “natural” (70). If a complication of a vaccination is rare, perhaps even exceedingly rare, but it is recognized as being possible and *known by the recipient of the vaccination to be possible*, then it could be argued that it represents a “reasonably foreseeable complication.” As such, according to the guideline, it would be acceptable to consider such a death as a natural death. If, on the other hand, death results from a medical intervention that had been presented to the patient as a totally “safe and effective” therapy, without any known risks for adverse effects, a natural MOD ruling may not be as appropriate. This highlights the extreme importance of “informed consent” regarding vaccinations (and other medical therapies/interventions).

CONCLUSION

Although not particularly common, seizure-related deaths are not rare. Most forensic pathologists investigate numerous such deaths during their careers. For every suspected seizure-related death, it is important for the forensic pathologist to attempt to identify the underlying cause of the seizure, since the identification of an etiology is necessary for appropriate cause and manner of death certification. Seizure disorders may be related to trauma, febrile illnesses, toxicologic or metabolic disturbances, natural disease with

structural/anatomic brain lesions, or epilepsy, where an anatomic or other cause cannot be elucidated. Post-vaccination seizures are a well-known but little-discussed entity. When a new-onset seizure disorder occurs following vaccination, and a neurologic work-up is negative for another explanation for the seizure, it is reasonable to conclude that the seizures are most likely due to an adverse reaction to the vaccination. If death occurs as a result of such seizures, it is likewise reasonable to implicate the vaccination as an underlying or contributing COD. In this report, two cases of post-COVID-19 vaccine new-onset seizures are presented. In one case, the ME released jurisdiction for death certification, and the PCP chose to not include the vaccination as a contributing COD. In the second case, the COVID-19 vaccination, along with a simultaneous influenza vaccine, was considered contributory to the seizure-related death, along with other natural disease processes.

The cases serve to illustrate the difficulties encountered when attempting to certify such deaths, especially with regard to the available medical literature regarding adverse vaccine reactions, much of which appears, on initial evaluation, to offer contradictory conclusions. While it is true that temporal association between a vaccination and an adverse event, such as a seizure (and subsequent death), does not confirm causality, the temporal relation remains an important piece of evidence when attempting to determine if a particular adverse reaction might be linked to a vaccination. It is especially important for forensic pathologists to evaluate each case on an individual basis, recognizing that the conclusions of various population-based statistical studies do not necessarily apply to individual cases. When a temporal association between seizures and vaccination exists, and there is no other explanation for the seizure disorder (via clinical work-up and/or neuropathological examination at autopsy), then it is reasonable to link the seizure (and death) to the vaccination.

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