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【 CASE REPORT 】

Delayed Vasovagal Reaction with Reflex Syncope Following COVID-19 Vaccination

Bonpei Takase[1,2], Katsumi Hayashi[1], Satoko Takei[1], Tetsuya Hisada[1], Nobuyuki Masaki[2] and Masayoshi Nagata[1]

Abstract:
Coronavirus disease 2019 (COVID-19) has become a pandemic, and vaccines remain the only effective tools available for ending it. However, their side effects, such as syncope, which mimics sudden cardiac death, are serious concerns. We herein report 6 cases of delayed vasovagal syncope and presyncope (VVR) caused by COVID-19 vaccination among 25,530 COVID-19 patients. The prevalence of delayed VVR due to COVID-19 vaccination was 0.026%. In addition, no delayed VVR was found among 17,386 patients who received the influenza vaccine. Delayed VVR is likely to be overlooked if medical staff are not aware of this symptom. This report provides significant information regarding effects of COVID-19 vaccination.

Key words: vasovagal response, SARS-CoV-2 vaccine, side effect, anxiety autonomic reflex

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Introduction

Coronavirus disease 2019 (COVID-19) is now a pandemic and a worldwide problem. The COVID-19 vaccine is a key factor in ending this pandemic. In most countries, vaccines manufactured by Pfizer and Moderna are used. Adverse side effects of COVID-19 are a serious problem. In extensive national vaccination programs, severe adverse events and even sudden unexpected deaths occur (1).

Among the COVID-19 vaccine's side effects, it is important to remember that some fetal side effects may also occur. However, anxiety and fear of the novel COVID-19 vaccine have been reported to induce a vasovagal reaction (VVR) (2), which can lead to presyncope and syncope.

VVR causing reflex syncope and presyncope is common during blood sampling and vaccination (3). VVR in blood sampling occurs mostly during and immediately after blood sampling or needle puncture, typically within 10-15 minutes. Similar to blood sampling, the immediate form of VVR has also been observed during vaccination (4). However, the delayed form of VVR has not been fully investigated, as most vaccine adverse events have been identified at the vaccine injection sites (5). Many vaccine adverse events occurring outside of vaccine sites are not likely to be recorded. Usually, a delayed form of VVR has been reported during blood sampling (5, 6).

In previous case series, delayed VVR was defined according to reports on blood donors (5, 7), including a general feeling of discomfort, light headedness, dizziness, yawning, nausea, sweating, pallor, unclear thinking, and weakness with anxiety and visual disturbance leading to syncope (fainting) or presyncope (near fainting). This takes place on-site or off-site of the vaccine injection (approximately 10 to 15 minutes after vaccine injection), as the reported presence of on-site VVR-related syncope markedly decreased within 10 minutes after whole blood donation (5, 8). In those reports, to diagnose delayed VVR, symptoms were weighed more than the actual vital signs, such as heart rate and blood pressure, as real-time vital signs of VVR events are not always available at the time of the symptom onset outside the vaccine sites.

In particular, in syncope with delayed VVR, the cardioinhibitory type of VVR [cardioinhibitory response (CI)] seems more serious than the vasodepressor type of VVR [vasodepressor response (VD)], even though previous studies have shown that both types pose a sizable risk of inducing adverse outcomes (9). However, since CI manifests as car-

[1]Division of Cardiology, Iruma Heart Hospital, Japan and [2]Department of Intensive Care Medicine, National Defense Medical College, Japan
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Correspondence to Dr. Bonpei Takase, dui1577@db3.so-net.ne.jp

diac arrest and advanced atrioventicular (AV) node blocks that might lead to sudden cardiac death, CI has been considered more serious than VD (9). Thus, it has been postulated that the delayed form of VVR syncope may cause CI.

To date, the features of COVID-19 vaccine-induced delayed VVR have not been fully clarified. We herein report six cases of syncope or presyncope experienced among 25,530 recipients whose symptoms did not occur immediately after the administration of COVID-19 vaccine manufactured by Pfizer. Informed consent for their inclusion in this study was obtained from all patients.

Case Reports

Case 1

A 26-year-old man without comorbidities had a syncope episode at the first dose of Pfizer's COVID-19 vaccine. This episode occurred approximately 30 minutes after vaccine injection without prodrome when he was walking back to the parking lot after the 15-minute observation period. The patient promptly recovered after lying on the ground. His blood pressure was 90/60 mmHg, and his pulse rate was 39 bpm, which lasted for over 20 seconds. The patient was eventually taken to the emergency room (ER). After 25 minutes of observation in the supine position, the patient fully recovered with a blood pressure of 118/70 mmHg and heart rate of 64 bpm. After recovery, the patient denied having any stress or unusual conditions after leaving the vaccine site.

Case 2

A 22-year-old man with no prior health problems complained of dizziness at 17 minutes after the first dose of Pfizer's COVID-19 vaccine. The patient suddenly collapsed on the floor without any prodrome. His history showed that he had suffered syncope at the time of influenza vaccination at another hospital, which he had not declared before received the COVID-19 vaccine because he had almost completely forgotten this episode. His blood pressure was 80/60 mmHg, and his pulse rate was 38 bpm, which lasted for at least 20 seconds. He was brought to the ER. After 40 minutes of observation in the supine position, the patient fully recovered.

Case 3

A 20-year-old woman complained of presyncope with dimming of vision and cold sweating 40 minutes after receiving the second shot of Pfizer's COVID-19 vaccine when she returned to her vehicle. Her medical history was unremarkable. Her blood pressure was 90/60 mmHg, pulse rate was 60 bpm, and an electrocardiogram (ECG) showed a normal sinus rhythm in the supine position. After 30 minutes of bed rest, she felt well again, and her blood pressure returned to 130/80 mmHg with a pulse rate of 80 bpm.

Case 4

A 17-year-old girl reported dimming of vision and presyncope 10 minutes after her first shot of Pfizer's COVID-19 vaccine. Her blood pressure was 95/60 mmHg, and her pulse rate was 58 bpm. An ECG showed sinus rhythm. Her medical history was not contributory. Hypotension continued in the supine position, and 250 mL intravenous rapid infusion of normal saline was performed. Her blood pressure increased to 101/57 mmHg, and her pulse rate was 71 bpm and regular. She felt completely well.

Case 5

A 19-year-old man complained of dizziness with dimming of vision, compatible with presyncope, in the parking lot 25 minutes after the first dose of Pfizer's COVID-19 vaccine. The patient was placed in the supine position. His blood pressure was 105/56 mmHg, and his pulse rate was 56 bpm. His medical history was unremarkable. His condition stabilized after lying down for 30 minutes. His blood pressure increased to 122/73 mmHg, and his pulse rate was 70 bpm.

Case 6

A 35-year-old man presented with dimming of vision and cold sweating 16 minutes after receiving the second shot of Pfizer's COVID-19 vaccine. He lost consciousness, and his radial pulse was not palpable. His ECG showed a junctional rhythm of 39 bpm for more than 20 seconds. Intravenous atropine sulfate (0.5 mg) was immediately administered. He completely recovered, and his ECG showed normal sinus rhythm. His blood pressure increased to 120/70 mmHg, and his pulse rate was 70 bpm. He had no history of blood phobia before the vaccination, but he had previously experienced VVR during blood sampling. Otherwise, the patient's history was unremarkable, and he recovered completely.

In our institution, we took a detailed history of the side effects of any vaccination before administering Pfizer's COVID-19 vaccine, especially with regard to VVR. In patients with a history of VVR, we administered the vaccine in the supine position and took all possible preventative measures to avoid VVR. Since VVR related to syncope causes body collapse, we postulate that maintaining the supine position during the administration of the vaccine, which prevents subsequent collapse, can alleviate patients' fear and anxiety regarding vaccine injection. Therefore, the patients were kept in the supine position to make them more comfortable.

Pfizer's COVID-19 vaccine was administered to 25,530 people until November 10, 2021. In this period, we experienced the abovementioned six cases of delayed VVR. The calculated prevalence of delayed VVRs in Pfizer COVID-19 vaccination at our institution was 0.026%. Defining delayed VVR using the stricter criteria proposed by Kamel et al. (6), 5 of these 6 cases met the criteria, indicating a prevalence of 0.022%. The clinical characteristics of these six cases are summarized in Table. One case of immediate VVR follow-

Table. **The Clinical Characteristics of These Six Cases.**

Case No.	Sex	Age	Time to VVR	Past history of VVR	CI	VD or Mixed	Medication
No.1	M	26 y/o	30 min	None	Present	None	None
No.2	M	22 y/o	17 min	Present	Present	None	None
No.3	F	20 y/o	40 min	None	None	Present	None
No.4	F	17 y/o	10 min	None	None	Present	Normal saline DIV
No.5	M	19 y/o	25 min	None	None	Present	None
No.6	M	35 y/o	16 min	Present	Present	None	Atropine IV

M: male, F: female, y/o : years old, CI: cardioinhibitory response, VD: vasodepressor response, VVR: vasovagal response, IV: intravenous injection, DIV: intravenous transfusion

CI is defined as decreased heart rate (less than 40 bpm for at least 20 seconds) with hypotension during syncope or presyncope, while VD is defined as hypotension without decreased heart rate (not less than 40 bpm) during syncope or presyncope, and mixed type was defined as hypotension with a short duration of heart rate decrease (less than 40 bpm for less than 20 seconds) (reference 9).

ing COVID-19 vaccination was observed in a 29-year-old man who fainted immediately after vaccine injection despite no predictive history. We reviewed the medical records in our institute for the past 10 years and found no cases of acute or delayed VVR among 17,386 influenza vaccinations.

Discussion

In this case series, six patients showed delayed VVR that met the definition proposed in previous reports (5, 7). Among the VVRs related to blood donation, immediate and delayed VVR have been reported (3). Even though immediate VVR in vaccination is well understood, there are few reports on the association between delayed VVR and vaccination, especially in the case of the COVID-19 vaccine.

Based on previous reports (5, 7), delayed VVR occurs after blood donation outside the collection site, typically within 12 hours after phlebotomy (5). The definition of delayed VVR in blood donors was described in this vaccine report. All six of our cases met the criteria for delayed VVR proposed previously. However, Kamel et al. (6) proposed stricter criteria for delayed adverse events, including VVR, including an onset time >15 minutes after the procedure. Even when using Kamel's strict delayed criteria, five of the six patients still met the criteria.

One of the most important observations in these case series was as follows: there was no recent past history of VVR-related syncope despite careful history taking as shown in Table. These two patients did not provide their history because their prior episodes had occurred long before the current episodes. Since we did not find any characteristics that were associated with the induction of VVR-related syncope after administering Pfizer's COVID-19 vaccine, it is reasonable to assume that our medical staff failed to perform preventive measures for VVR at the time of COVID-19 vaccination in these patients. In addition, since delayed VVR occurred after the usual observation time period of 15 minutes in 5 out of 6 patients in our series, delayed VVR may have been overlooked, and there was a possibility that syncope or presyncope might have taken place outside the medical center. In addition, since delayed VVR has been reported to cause trauma in cases of blood donation (10), it might also have caused serious problems if delayed VVR had occurred outside the medical center.

Another important observation was that half of the patients showed a CI response. Since a CI response mimics cardiac arrest, patients may be prone to sudden cardiac death if they cannot lie down on the floor or if they remain in an upright position for any reason when they collapse. The recently developed COVID-19 vaccine has possibly been associated with sudden death in several countries. Such pathophysiologies as CI cannot be completely ruled out in these cases. There have been no reports of sudden cardiac death with other vaccines (11). However, seven unexpected deaths after the Papillomavirus recombinant vaccine (HPV) (Gardasil®, Merck, Whitehouse Station, USA) were reported. As a result, the notion that COVID-19 vaccination alone may cause unexpected sudden death thus only remains speculative, but nevertheless this possibility should still be kept in mind. However, since there is no evidence concerning the relationship between VVR and unexpected death caused by a vaccine, it is difficult to associate VVR induced by COVID-19 vaccination with sudden death.

The prevalence of VVR in this study was in agreement with a previous report (12). Syncopal episodes are anxiety-related symptoms, and syncope is frequently observed in children, young adults, and the elderly (12). According to experiences in the US (12), clinical characteristics of anxiety-related adverse events include tachycardia, hyperventilation, dyspnea, chest pain, paresthesia, headache, pallor, and syncope. The total incidence of anxiety-related symptoms after COVID-19 vaccination is 164 times higher than that with the usual influenza vaccine (12). Syncopal episodes are thought to be relatively common with COVID-19 vaccination. Several studies have reported on the incidence of immediate VVR with syncope. HPV, the quadrivalent meningococcal conjugate vaccine (MCV4) (Menactra®, Sanofi Pasteur, Swiftwater, USA), and the acellular pertussis vaccine (Tdap) (Adacel®, Sanofi Pasteur; Boostrix®, GlaxoSmithKline Biologicals, Research Triangle Park, USA) are

also relatively new vaccines, like COVID-19 (11). The syncopal adverse event rate among these vaccines is 0.0035-0.078% (3, 11), which are equal to or lower than that of immediate VVR with syncope in COVID-19 patients (reportedly 0.023-0.082%) (12, 13). Compared to the prevalence of immediate VVR with syncope between COVID-19 and HPV, MCV4, and Tdap vaccines, the precise incidence of delayed VVR in the other vaccines has not been well reported. Thus, the results of the delayed COVID-19 described in this report may therefore be a novel finding. However, as mentioned above, the immediate or total syncopal adverse rate in COVID-19 vaccine is speculated to be the same as the rates with the HPV, MCV4, and Tdap vaccines.

The mechanisms underlying delayed VVR after COVID-19 vaccination remain unclear. However, since the mechanisms underlying delayed VVR-related syncope in blood donors have been reported to be associated with anxiety-related sympathetic overdrive or volume depletion, the COVID-19 vaccine-associated mechanisms may be similar. In addition, delayed VVR following COVID-19 vaccination may have been caused by stress or anxiety-related mechanisms rather than the vaccine itself, as VVR-related syncope has been reported with other vaccines (5, 7, 8, 11). Even in blood donor-related delayed VVR, the mechanism that contributes to the difference between acute and delayed VVR has not been clarified, it is difficult to elucidate the etiology of delayed VVR in COVID-19 vaccination.

To prevent VVR, hydration (e.g. drinking water), pain management during the procedure, and muscle tension maneuvers have been proposed (14, 15). These preventive measures are also effective in treating reflex syncope. Considering these observations, the possible mechanism underlying delayed VVR by COVID-19 vaccination might be prolonged and exaggerated sympathetic nerve activity caused by anxiety and fear regarding the new COVID-19 vaccine. If our speculation regarding the delayed VVR mechanism is correct, this pathophysiology might be similar to that of reflex syncope.

However, the differences in the mechanisms underlying acute and delayed VVR cannot be explained by our case series. This is a limitation of this case report, and further research to clarify this mechanism will be necessary. Understanding the associated preventative measures and mechanisms underlying delayed VVR induced by COVID-19 vaccination is considered useful for safely administering the COVID-19 vaccine at vaccination sites. In this regard, this report provides significant information supporting the ongoing COVID-19 vaccination program.

Furthermore, adverse side effects of COVID-19 vaccine are associated with immunization stress-related responses. If the coronavirus pandemic subsides and anxiety surrounding COVID-19 vaccination is reduced, the incidence of delayed VVR may be decreased. A further observational study in the future following up episodes of delayed VVR after COVID-19 vaccination is necessary. In addition, since delayed VVR may occur much later after vaccination than was observed in our case series, abstaining from driving or engaging in other potentially high-risk behaviors on the day of vaccination is recommended.

The authors state that they have no Conflict of Interest (COI).

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