Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

AUTHOR CONTRIBUTIONS

LV reviewed the data, updated the figures and drafted the response. The other authors reviewed the manuscript prior to submission.

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The statistical risk of diagnosing coincidental acquired hemophilia A following anti-SARS-CoV-2 vaccination

We read with interest the case report by Radwi and Farsi of a 69-year-old man with acquired hemophilia A (AHA) following vaccination with the Pfizer-BioNTech SARS CoV-2 mRNA vaccine.[1] The publication prompted us to perform a survey within the Working Party Haemostasis of the Swiss Society of Hematology to detect similar cases in Switzerland. The survey led to the identification of three cases of AHA in Switzerland between December 23, 2020 and April 30, 2021.

The first patient is an 85-year-old man who developed transient pain and swelling in the right forearm 1 week after the first dose of the Moderna COVID-19 (mRNA-1273) vaccine and multiple mild hematomas of the right thigh and spontaneous joint bleeding in both knees. After the second dose, the patient noted worsening of the hemorrhagic complications. His past medical history included arterial hypertension, coronary bypass surgery, peripheral artery disease, and renal and carotid artery stenosis treated with low-dose aspirin. The patient was hemodynamically stable; abdominal palpation revealed right lower quadrant abdominal tenderness. Computed tomography (CT) showed a large hematoma of the right iliopsoas muscle and free fluid in the right lower abdomen. Laboratory results revealed rapidly worsening anemia suggesting active bleeding. Prothrombin time (PT) was normal, but the activated partial thrombin time (APTT) showed a significant prolongation (49s; normal range 27–35s). The APTT mixing study was typical for a delayed-acting inhibitor of coagulation. Factor VIII-activity (FVIII:C) was not detectable (normal range 50–150%) and a FVIII inhibitor was found with a titer of 2.2 BU/ml, prompting the diagnosis of an AHA. Anti-SARS-CoV-2 spike IgG were 42.6 BAU/ml and anti-nucleocapsid IgG were negative. The screening for malignancies and autoimmune diseases was negative. Therapy with recombinant activated factor VII (rFVIIa) was initiated and later switched to activated prothrombin complex concentrate (APCC). An immunosuppressive therapy with prednisone 100 mg/d was started and subsequently an anti-CD20 treatment with rituximab was added, with no immediate response. Three and a half weeks after diagnosis, the patient experienced acute gall bladder rupture with active arterial bleeding. Due to the severe bleeding risk and the critical clinical condition, surgery was not possible and arterial coiling was performed which, however, only transiently stopped the bleeding. The patient refused any further intervention and died shortly after that.

The second patient is an 86-year-old woman with increasing shortness of breath days after an incidental fall with chest and shoulder contusion. She had received the second dose of the Moderna COVID-19 (mRNA-1273) vaccine 3 weeks prior to the fall. Her past medical history was remarkable for moderate to severe aortic valve

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stenosis treated non-surgically and pacemaker implantation for third-degree atrioventricular block. The patient was treated with low-dose aspirin. A chest CT scan revealed right-sided hemothorax and fractures of ribs 9–11. A chest drain was placed leading to a large subcutaneous effusion. Laboratory hemostasis tests showed a regular PT but a prolongation of the APTT, with an APTT mixing study typical for a delayed-acting inhibitor of coagulation. FVIII:C was 23%, and a low-titer FVIII inhibitor of 1.01 BU/ml was detected. Anti-SARS-CoV-2 spike IgG titer was 150 BAU/ml. A 3-day treatment first with rFVIIa, and later with APCC was needed to control local bleeding and to remove the chest drain. The further course was uneventful and after 17 days of treatment with oral prednisone (1 mg/kg) FVIII:C increased to 178%. An extensive screening for cancer, chronic infectious diseases, and autoimmune diseases other than AHA was negative and the patient was discharged.

The third patient is a 72-year-old woman whose past medical history was characterized by multiple comorbidities including arterial disease, for which she was taking low-dose aspirin. Two weeks after having received the first dose of Moderna COVID-19 (mRNA-1273) vaccine, she started noticing extensive cutaneous bruising. Ten days after the onset, she presented to the emergency department with multiple large cutaneous hematomas, a hemoglobin of 56 g/L (normal range 120–160 g/L), and a prolonged APTT of 184s (normal range 25–37s). Further evaluation prompted the diagnosis of AHA by revealing a delayed-acting inhibitor in the APTT mixing study, a non-detectable FVIII activity, and a FVIII inhibitor of 12.4 BU/ml. Screening for malignancy, chronic infectious diseases, and autoimmune disorders was negative. Anti-SARS-CoV-2 spike IgG titer was 83 BAU/ml. A 7-day treatment with rFVIIa and tranexamic acid was administered and in parallel immunosuppression was started with prednisone 100 mg/d and rituximab 375 mg/m^2 weekly (4 doses). The bleeding tendency improved remarkably 1 week after the first dose of rituximab and after the third dose of rituximab, FVIII activity increased to 5% while FVIII inhibitor decreased to 5.6 BU/ml.

We reported all three cases to the national drug authority (Swissmedic) per Swiss law.

It is currently unknown whether the COVID-19 vaccines could trigger the onset of AHA or whether the association should be considered coincidental. We, therefore, performed an online survey within the Working Party Haemostasis of the Swiss Society of Hematology. Patients with AHA following COVID-19 vaccination were included if they had received at least one dose of an mRNA vaccine before March 31, 2021, and if the onset of AHA was no later than April 30, 2021. Written informed consent for publication was obtained from all patients. Epidemiological data on the current population census and administered doses of the COVID-19 vaccines were provided by the Swiss Federal Statistical Office.[2,3] According to the 2020 census, the Swiss population is estimated to be 8,667,000, of which 1,630,000 (18.8%) are over age 65. The incidence of AHA in Europe is believed to be 1.5 to 6 per 1.000.000, and 85% of the patients are older than 65 years.[4–6] Based on these data, we would expect 11 to 44 AHA cases per year in the age group >65 years in Switzerland.

As of March 31, 2021 only the COVID-19 mRNA vaccines by Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) were available in Switzerland, and the total number of Swiss residents aged 65 years or older who had received one and two vaccine doses was 283,650, and 446,618, respectively. The three above-mentioned cases of AHA were considered potentially related to the vaccine. When testing for the statistical probability by which the COVID-19 vaccine and AHA would randomly coincide in individuals >65 years, we assumed that AHA cases are distributed equally over the year, that the two vaccine doses are given at an interval of 28 days, and that a specific symptom might be attributed to the vaccination when occurring within 28 days after either of the two doses. The observed AHA incidence in the vaccinated >65-years-old population was 4.1 per million, which is a 4-fold increase compared to the historical overall incidence of 1.5 per million, but is exactly what can be expected when calculating with an overall AHA incidence of 6 per million. Due to the low numbers of events, these data remain, however, speculative and warrant further investigation.

With regard to global data, up to May 9, 2021, VigiBase®, the World Health Organization's global pharmacovigilance database of suspected adverse drug reactions, has gathered 25,187,619 cases of which 316 are suspected AHA. Of these, 11 cases were reported in association with vaccines (of the anatomical therapeutic chemical group J07), including six cases with COVID-19 vaccines (four with the Pfizer-BioNTech SARS CoV-2 mRNA vaccine and two with the Moderna COVID-19 [mRNA-1273] vaccine). Suspected AHA with COVID-19 vaccines developed with a median delay of 26 days (ranging from 3 to 30 days); 4 cases did not recover, while 2 were recovering at the time of reporting.

In the context of the current worldwide vaccination campaign, the onset of an extremely unusual disease such as AHA is likely to temporally coincide with the vaccination even without a causative relationship, and we advise caution when attributing rare diseases to the administration of COVID-19 vaccine in the absence of scientific evidence proving the pathophysiological correlation. Unlike vaccine-induced immune thrombotic thrombocytopenia (VITT), in which the mechanism of disease has recently been described, the association of AHA with vaccines tends to be descriptive and is not yet fully understood.[7–11]

Limitations of our study are the relatively short observation period of 4 months, which might not be sufficient to detect very rare side effects, and the possible underreporting of AHA in the survey as not all AHA cases might be detected, and some patients with mild AHA could have spontaneous remission without a diagnosis being made.[12] In conclusion, while we cannot definitively rule out a causative relationship between anti-SARS-CoV-2 vaccines and AHA, our data might help put the risk of a very rare, and yet unproven adverse event following immunization (AEFI) into perspective. AEFIs must be weighed against the huge benefit of this unprecedented vaccination campaign that is saving millions of lives worldwide.

KEYWORDS

acquired hemophilia A, AHA, COVID-19, hemostasis, SARS-CoV-2 vaccine

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

MGC, RB, and AC wrote the first draft of the manuscript. All authors critically read, discussed, and corrected the manuscript.

ACCOMPANYING STATEMENT

Data from spontaneous ADR reporting are inhomogeneous as a result of different reporting policies worldwide and are vulnerable to underreporting and reporting bias. The information is therefore not homogeneous, at least with respect to origin and likelihood that the pharmaceutical product caused the adverse reaction. Conclusions drawn based on the post-marketing data in VigiBase are those of the authors and not those of the Uppsala Monitoring Centre, National Centres, or the World Health Organisation.

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