

Vaccine associated benign headache and cutaneous hemorrhage after ChAdOx1 nCoV-19 vaccine: A cohort study

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Objectives: Fatal complications have occurred after vaccination with ChAdOx1 nCoV-19, a vaccine against Covid-19. Vaccine-induced immune thrombotic thrombocytopenia (VITT) with severe outcome is characterized by venous thrombosis, predominantly in cerebral veins, thrombocytopenia and anti-PF4/polyanion antibodies. Prolonged headaches and cutaneous hemorrhages, frequently observed after the ChAdOx1 nCoV-19 vaccine, have therefore caused anxiety among vaccinees. We investigated whether these symptoms represent a mild form of VITT, with a potential for aggravation, e.g. in case of a second vaccination dose, or a different entity of vaccine complications. *Materials and methods:* We included previously healthy individuals who had a combination of headache and spontaneous severe cutaneous hemorrhages emerging after the 1st dose of the ChAdOx1 nCoV-19 vaccine. Twelve individuals were found to meet the inclusion criteria, and a phone interview, cerebral MRI, assessment of platelet counts, anti PF4/polyanion antibodies and other laboratory tests were performed. *Results:* None of the symptomatic vaccinees had cerebral vein thrombosis, hemorrhage or other pathology on MRI. Platelet counts were within normal range and no anti-PF4/polyanion platelet activating antibodies were found. Moreover, vasculitis markers, platelet activation markers and thrombin generation were normal. Furthermore, almost all symptoms resolved, and none had recurrence of symptoms after further vaccination with mRNA vaccines against Covid-19. *Conclusions:* The combination of headaches and subcutaneous hemorrhage did not represent VITT and no other specific coagulation

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disorder or intracranial pathology was found. However, symptoms initially mimicking VITT demand vigilance and low threshold for a clinical evaluation combined with platelet counts and D-dimer.

Keywords: ChAdOx1 nCoV vaccine—Adverse event—Headache—Cutaneous hemorrhage

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Introduction

To control the Covid-19 pandemic, mass vaccination against the SARS Cov-19 virus has been implemented worldwide after confirming the safety of vaccines in phase 2 and 3 studies, as well as interim analyses.^{1–5} However, severe complications after vaccination with the viral vector COVID-19 vaccine ChAdOx1 nCoV-19 have occurred. A novel clinical syndrome, vaccine-induced immune thrombotic thrombocytopenia (VITT), is characterized as a vaccine-induced variant of autoimmune heparin-induced thrombocytopenia (aHIT) with thrombosis, thrombocytopenia and high anti-PF4/polyanion antibodies.^{6–8} Headache is the most frequent presenting symptom of VITT.⁹ VITT primarily affected young, previously healthy individuals and the outcome was poor.¹⁰ Pre-VITT syndrome has also been described which is characterized by thrombocytopenia and severe headache without associated thrombosis following vaccination with the ChAdOx1 nCoV-19 vaccine.¹¹ This has caused uncertainty among health authorities and skepticism to the ChAdOx1 nCoV-19 vaccine in the population. In Norway, vaccination with ChAdOx1 nCoV-19 was halted on March 11th 2021, and the national health authorities recommended seeking immediate medical attention if vaccinees experienced severe headaches, blurred vision or cutaneous hemorrhages after vaccination.

The occurrence of cutaneous hemorrhages, often accompanied by headaches, has caused a pronounced anxiety in individuals experiencing these symptoms, as they resemble the early stages of VITT. Nevertheless, it is not clear whether these symptoms represent VITT with a potential for aggravation in case of a second vaccination dose, or a different entity of vaccine complications. Our aim was to investigate whether individuals experiencing strong side effects with headaches combined with extensive cutaneous hemorrhages presented with radiological and laboratory findings were indicative of VITT, a milder form of the syndrome or a different entity of vaccine complications affecting hemostasis.

Methods

Ethics

The study was conducted according to the World Medical Association Declaration of Helsinki and was approved by the Regional Ethics Committee of South-Eastern

Norway, approval number 124170. All study participants signed a written informed consent.

Inclusion criteria and recruitment of study participants

Inclusion criteria were prolonged headaches (<3 days) or late onset headache of unusual character for the participant, combined with spontaneous cutaneous hemorrhages covering a larger area of the body (a part of a limb or abdomen/truncus) emerging after the first dose of ChAdOx1 nCoV-19 vaccination. None had previous illnesses or were taking medication with the potential to affect hemostasis. The participants were recruited through the Norwegian Corona Cohort, a population-based cohort study that follows 197 000 individuals through the pandemic. In Norway, the ChAdOx1 nCoV-19 vaccine was primarily administered to health care workers. On March 24th and 25th 2021, an invitation by e-mail was sent to 546 participants, recently vaccinated with ChAdOx1 nCoV-19 in the greater Oslo area. In the invitation, we asked vaccinees who met the inclusion criteria to answer an online screening questionnaire.

Data collection

Study participants who met the inclusion criteria completed the screening questionnaire about vaccination date, description, localization and extension of skin bleeds and information about duration of symptoms. Symptoms were specified bruises and petechiae.

To confirm that the inclusion criteria were fulfilled, a detailed telephone interview was conducted with all study participants to collect precise description of symptoms and to assess the past medical history. Participants who still were considered to meet the inclusion criteria after the interview were invited to give blood samples and to perform Magnetic Resonance imaging (MRI) with venography. A follow-up telephone interview was conducted after 8 months, assessing the clinical course of the studied symptoms and information about potential side effects of further COVID-19 vaccination.

Magnetic resonance imaging

Study participants were screened for cerebral sinus vein thrombosis (CSVT) with MRI. An MRI screening protocol was utilized, including phase-contrast MRI venography

(PCA) and susceptibility-weighted imaging (SWI). All MRIs were assessed by experienced neuroradiologists.

Immunoassays and functional testing

Serum antibodies to platelet factor 4 (PF4)/PVS (polyanionic polyvinyl sulfonate) were tested by LIFECODES PF4 IgG ELISA immunoassay (Immucor, Waukesha, WI), according to the manufacturer's instructions (dilution 1:50; optical density (OD) cutoff value ≥ 0.400). Positive samples in ELISA were tested by heparin-induced multiple electrode aggregometry (HIMEA) on the multiplate analyzer (Dynabyte Medical, Germany) as reported previously.⁷ Additionally, sera were tested with a platelet activation test, the PF4-dependent P-selectin expression assay (PEA), modified from Samuelson Bannow et al.¹² Briefly, pooled platelets from two random blood donors were incubated with 10 $\mu\text{g}/\text{mL}$ PF4 and patient sera, and level of platelet activation was measured by P-selectin expression using flow cytometry.

Blood counts, coagulation parameters and vasculitis biomarkers

Routine laboratory tests were performed, including platelet count, hemoglobin level, leukocyte count, D-dimer, fibrinogen, and C-reactive protein. Anti-neutrophil cytoplasmic antibodies (ANCA) were tested both with immune fluorescence for P-ANCA and C-ANCA and ELISA tests specific for proteinase 3 and myeloperoxidase ANCA. Antinuclear antibody (ANA) screening was performed and if positive, tests for anti-ENA and anti-dsDNA were assessed in addition to Anti-C1q antibodies.

Thrombin generation

Thrombin generation was measured in citrated platelet poor plasma (PPP) using the Calibrated Automated Thrombogram (CAT) TGA (Diagnostica Stago, Asnières-sur-Seine, France) with the Thrombinoscope software (Thrombinoscope BV, Maastricht, The Netherlands). Plasma from the anticoagulated participant with newly diagnosed DVT was not analyzed as anticoagulant would influence the thrombin generation results. PPP from the included vaccinated individuals and pooled plasma from normal controls were run in triplicates. The PPP reagent containing 5 pM tissue factor (TF) and 4 μM phospholipids (Diagnostica Stago, Asnières-sur-Seine, France), was used to initiate thrombin generation.^{13,14}

Platelet activation assays

Sodium citrated samples from patients and controls were spun for 20 min at $200 \times g$ and platelet rich plasma was collected. We assessed surface expression of CD62 (P-selectin) and CD63 (GP53) on resting platelets to evaluate spontaneous activation and on stimulated platelets as a

measure of the residual platelet activation potential, as reported previously.¹⁵

Covid-19 serology

Serum antibodies to spike and nucleocapsid proteins from SARS-CoV2 were measured with the Roche Elecsys platform and with an in-house bead-based assay for IgG antibodies to full length recombinant proteins.

Results

Recruitment and clinical presentation

18 individuals responded to meet the inclusion criteria with the relevant prolonged symptoms and returned the screening questionnaire. Twelve individuals met the inclusion criteria after the interview and were included in the study, Characteristics of the study participants are listed in [Table 1](#).

Median number of days from vaccination to blood sampling were 26 (range 10 to 37) and median number of days from vaccination to MRI were 24 (range 14 to 37). Headaches had a median onset 1.5 days after vaccination and lasted for a median of 2.8 weeks ([Table 1](#)). The prolonged headache intensity was mild in eight study participants, moderate in three and strong in one. Common for all was that headaches were not common or known for the participants prior to the vaccine. Spontaneous cutaneous hemorrhages, in form of bruises or petechiae, appeared within the first two weeks after vaccination and lasted for up to four weeks. They were mainly present on upper and lower extremities. Three study participants had bruises on truncus and one had facial petechiae. None of the study participants had a previously known bleeding condition. At the time of blood sampling, four study participants were still developing cutaneous hemorrhages and at the time of MRI, six study participants had ongoing headaches. On the 8 month follow up interview 10 participants were asymptomatic, while one participant experienced recurring cutaneous hemorrhages, and another ongoing headaches. All participants apart from the one with ongoing cutaneous hemorrhages, had later received Covid-19 mRNA vaccines without experiencing prolonged headaches, cutaneous hemorrhages or other severe side effects.

MR venography

Eleven study participants were examined with phase-contrast MR venography (PCA) and susceptibility-weighted imaging (SWI), with additional sequences in four study participants on indication by the neuroradiologist. One MRI had been performed at a local hospital and the sequences included T2-FLAIR, T2-TSE, T1-MPRAGE, and contrast-enhanced T1-MPRAGE. No evidence of cerebral vein thrombosis, hemorrhage or other acute pathology was found in any of the study participants.

Table 1. Participant characteristics and symptoms.

Case No	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	43	40	32	32	32	31	28	45	30	48	32	42
Sex	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female
Date of first vaccination	11.03.21	10.03.21	26.2.21	8.3.21	22.2.21	11.3.21	10.3.21	5.3.21	22.2.21	2.3.21	25.2.21	4.3.21
Regular medication	IUD	Anti-histamine	Mini pill	Estrogen vaginal ring	Mini pill	None	Estrogen vaginal ring	None	Mini pill	Anti-histamine, Salbutamol	Levothyroxine	None
Ongoing symptoms at time of examination	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Previous heparin	Uncertain	No	No	No	LMWH	No	No	Uncertain	No	LMWH	No	LMWH
Covid-19 vaccination (2. and 3. Dose)	mRNA vaccine x 2	mRNA vaccine x 2	mRNA vaccine x 2	mRNA vaccine x 2	mRNA vaccine x 2	mRNA vaccine x 2	mRNA vaccine x 2	mRNA vaccine x 2	mRNA vaccine x 2	none	mRNA vaccine x 2	mRNA vaccine x 2
Headaches after mRNA vaccine	No	No	No	No	No	No	No	No	No	No	No	No
Clinical status at 8 mth. follow-up	No symptoms	No symptoms	Light headaches	No symptoms	No symptoms	No symptoms	No symptoms	No symptoms	No symptoms	Bruising	No symptoms	No symptoms

IUD: Intrauterine device; HA: Headaches; Pe: Petechiae; Br: Bruises; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin

Platelet immunology results

Anti-PF4-complex antibodies were detected in one study participant only (0.414 OD), with PF4/PVS IgG ELISA (Table 2). None of the study participant's sera, including the case with anti-PF4-complex antibodies detected, induced platelet aggregation in the HIMEA assay or platelet activation in PEA (with and without PF4).

Blood counts, coagulation parameters and vasculitis biomarkers

Platelet counts were within the normal range in all study participants, as were INR, aPTT, fibrinogen, D-dimer and CRP. Except for one participant with a weak positive anti-dsDNA, and another with borderline values of anti-ENA antibodies, all patients were ANA negative. No participants had anti-C1q antibodies (Table 2).

Thrombin generation

Mean lag time was 3.40 min (min-max 2.70-4.30). Mean peak thrombin concentration was 233 pM (min-max 180-303) and mean endogenous thrombin potential (ETP) was 1461 pM x minutes (min-max 1160-1905). No significant difference was found between our cases and pooled plasma from 13 healthy controls (Table 2).

Platelet activation

Measuring the degree of spontaneous activation, we found that the percent expression of CD62P and CD63 in the patient samples ($n = 7$) was similar to the percent expression in the control samples from healthy blood donors ($n = 6$), no significant differences were seen ($p = 0.79$ for CD62P and $p = 0.79$ for CD63). Examining the residual activation potential for the same activation markers, we found that all patients had a high capacity for platelet activation after stimulation with TRAP6. We found no significant differences compared to the normal controls from healthy blood donors ($p = 0.42$ for CD62P and $p = 1.0$ for CD63).

Covid-19 serology

None of the participants had positive nucleocapsid antibodies. All had positive Covid-19 spike protein antibodies.

Discussion

Prolonged symptoms of headaches and spontaneous cutaneous hemorrhages after ChAdOx1 nCoV-19 vaccine, as described in our study participants, may indicate VITT or pre-VITT syndrome. However, none of the study participants had thrombocytopenia, elevated D-dimer, significant levels of anti PF4/polyanion antibodies, positive platelet aggregation test, or cerebral vein thrombosis. Furthermore, thrombin generation was normal and

Table 2. Blood test results of the study participants and reference values or *healthy controls.

	Mean (min-max)	Reference values/healthy controls*
Platelet count (x 10 ⁹ /L)	272 (193-420)	145-390
Leucocyte count, nadir (10 ⁹ /L)	6.3 (4.5-7.5)	3.5-10
Hemoglobin (g/L)	13.2 (12.0-14.1)	11.7-15.3
D-dimer (mg/L)	0.24 (0.19-0.40)	<0.54
Fibrinogen (g/L)	2.59 (2.1-3.5)	1.9-4.0
INR	1.0 (0.9-1.3)	0.9-1.2
aPTT (seconds)	25 (22-28)	22-30
CRP (mg/L)	1.2 (0.6-4.0)	<4
PR3-ANCA (x10 ³ IU/L)	<2	<7
MPO-ANCA (x10 ³ IU/L)	<2	<7
Anti-ENA	Negative in all	
Anti-dsDNA(x10 ³ IU/L)	1	<15
Anti-C1q (x10 ³ IU/L)	3.2	<10
Thrombin generation ETP (n = 9)	1461 (1160-1905)	1307 (1129-1482)*
Thrombin generation peak (n = 9)	233 (180-303)	218 (139-273)*
Lag time (n = 9)	3.4 (2.7-4.3)	3.0 (2.3-4.7)*

vasculitis markers were all negative. Thus, VITT and pre-VITT syndrome could be ruled out as the cause of the symptoms, and there were no convincing indications for vasculitis or a coagulation disorder. This combination of symptoms may therefore represent a different entity of vaccine complication with an unknown pathomechanism.

When VITT is suspected, ELISA tests have shown to be a sensitive method to detect anti-PF4/polyanion antibodies and are recommended to confirm the diagnosis.¹⁶ Importantly, the gold standard to diagnose VITT is subsequent functional platelet aggregation and activation assays, to determine the ability of sera to activate platelets in a heparin-independent manner.¹⁷ However, prompt diagnosis and treatment are crucial to improve the outcome of VITT and it is recommended to start treatment if the other diagnostic criteria are present, i.e. adenoviral vector vaccine administered prior to symptoms, thrombocytopenia, thrombosis, and elevated D-dimer.^{6,8,17} One study participant had anti-PF4/polyanion antibody level just above cut off, but no platelet activation was detected. This may be an incidental finding as it has been demonstrated that anti-PF4/polyanion antibodies may be detected in 5–7% of healthy individuals.¹⁸

In all study participants, headache started within two-three days after vaccination, and the spontaneous cutaneous bleeds appeared within two weeks. Apart from one study participant who had minor, but persisting skin bleeds 8 months after vaccination and is still in hematological follow-up and assessment, the clinical picture regressed spontaneously in all. Symptoms of VITT and pre-VITT syndrome, however, usually start within 5–17 days, but also as late as 48 days after vaccination with ChAdOx1 nCoV-19. The majority of VITT patients have a severe disease progression with a high mortality rate.¹⁷ Pre-VITT syndrome with thrombocytopenia, strongly positive anti PF4/polyanion antibody results

and severe headache precedes VITT and treatment with intravenous immunoglobulins may improve the outcome.¹¹ In pre-VITT syndrome, headache is not caused by CSVT, but possibly by microthrombi or other factors not visible on an MRI. To distinguish pre-VITT syndrome from the syndrome described in our cohort is therefore of clinical importance.

Large safety studies have not reported increased incidence of venous thrombotic events (VTE) in individuals vaccinated with ChAdOx1 nCoV-19.⁴ However, an increased risk of VTE, including cerebral venous thrombosis, was reported in Denmark and Norway.¹⁹

Cutaneous hemorrhages are not reported as an adverse event in EMA's safety profile of the ChAdOx1 nCoV-19 vaccine,²⁰ nor in the Phase 2/3 studies.^{4,21} In congruence with our observations, a recent manuscript stresses that ChAdOx1 nCoV-19 was associated with a higher incidence of cutaneous hemorrhages than the Pfizer/Biontec and Moderna vaccines (3.2% versus 0.1%).²² In yet another published observational study with 500 individuals vaccinated with ChAdOx1 nCoV-19 vaccine, up to 10% reported cutaneous hemorrhages and 70% experienced headaches without other severe complications.²³ This may raise concerns that side effects after COVID-19 vaccination have been underreported by health authorities and pharmaceutical companies, contributing to the skepticism and hesitancy to COVID-19 vaccines, a major challenge to achieve high population-wide vaccination rates and thus efficient protection from the pandemic.^{24,25} All but one participant received successive doses of mRNA vaccines, and experienced no severe or prolonged symptoms thereafter.

This study has several limitations: MRI and laboratory examinations were not consistently performed at the peak of the symptoms. Therefore, mild thrombocytopenia or coagulopathy may have been missed. Clinical symptoms

were self-reported by study participants, rather than objectified. However, all study participants were health care professionals, as ChAdOx1 nCoV-19 vaccine in Norway was initially administered to this group. They all could precisely describe their cutaneous hemorrhages and other symptoms. MRI without contrast may not be the optimal assessment of CSVT. We did not want to expose the study participants to radiation from CT venography or give them gadolinium-based contrast, unless clinically indicated. Therefore, small thrombi may have remained undetected in this study.

Prolonged symptoms in study participants may have been caused by a strong antibody response to the vaccine, causing prolongation of symptoms. However, in samples collected after the first dose of ChAdOx1 nCoV-19, all study participants had an antibody response with significant variation of antibody levels, which does not confirm an overall strong response.

This study was set up due to the increasing awareness of VITT, a new and severe complication after vaccination with ChAdOx1 nCoV-19. The ongoing Corona study (www.koronastudien.no) made it possible to quickly distribute a questionnaire and select vaccinees with prolonged symptoms of headache and cutaneous hemorrhages, suggestive of VITT. The response rate was higher than expected with 18 positive replies after 546 persons had been approached. However, we cannot make assumptions about the true incidence of headaches in combination with cutaneous hemorrhages.

The clinical presentation with prolonged headaches and cutaneous hemorrhages in our study participants were initially similar to those in VITT patients, but the course of condition was different. While VITT patients rapidly declined clinically and often developed neurological deficits, due to intracranial pathology, the participants in our study had a mild course of disease and rarely needed treatment. Unlike VITT, radiological assessment did not demonstrate any signs of CSVT, or other related pathology and laboratory results ruled out thrombocytopenia and anti-PF4/polyanion antibodies. This is reassuring for the large group of individuals experiencing headaches and cutaneous hemorrhages after vaccination and suggests that thrombocytopenia and anti-PF4/polyanion antibodies are the keys to diagnose VITT. The study participants presented a characteristic combination of symptoms with headaches 1-5 days after vaccination and cutaneous hemorrhages appearing a few days later, possibly representing another vaccination induced syndrome with a benign course.

Conclusion

The clinical picture with prolonged headache and cutaneous hemorrhages associated with the ChAdOx1 nCoV-19 vaccine in our cohort initially resembled VITT, but the symptoms resolved spontaneously. These side effects

seem to represent a different entity of vaccine complications and further investigations are needed to understand the pathophysiology.

Declaration of Competing Interest

N.H.S. has received honoraria from Pfizer, BMS, and Bayer for lectures about management of anticoagulation treatment and bleeding.

P.A.H. has received research grants to institution from Bayer, Pfizer, SOBI, and Roche within area of bleeding disorders, and lecture honoraria, and honoraria for participation in advisory boards in the area of bleeding disorders from Takeda, SOBI, Bayer, Pfizer, Roche, Octapharma, NovoNordisk, CSL and BMS. He has received support for attending meetings from Takeda, Bayer, Roche, Pfizer, Octapharma, NovoNordisk, CSL and SOBI, and he is a member of executive committee of the ADVANCE group and ACHIEVE group, Bayer.

I.H.S. reports that her spouse is the CEO in Arctic-Zymes Technologies.

A.A. has received personal fees from Bayer, Boehringer Ingelheim, Roche, Allergan, Novartis and Teva.

K.S. has received personal fees from Bayer.

M.K.H.W. has received research grants from the South-Eastern Norway Regional Health Authority, and reports ownership of stock Biontech/Pfizer.

A.V.L.S., C.A., A.V., J.S.B., M.T.A., T.H.S. and M.S. have no conflicting interests.

CRedit authorship contribution statement

Nina Haagenrud Schultz: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Arne Vasli Lund Sørås:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Ingvild Hausberg Sørvoll:** Formal analysis, Methodology, Writing – review & editing. **Çigdem Akalin Akkøk:** Formal analysis, Methodology, Writing – review & editing. **Annette Vetlesen:** Formal analysis, Methodology, Writing – review & editing. **Jagjit Singh Bhamra:** Formal analysis, Methodology, Writing – review & editing. **Maria Therese Ahlen:** Formal analysis, Methodology, Writing – review & editing. **Pål Andre Holme:** Formal analysis, Methodology, Writing – review & editing. **Anne-Hege Aamodt:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Karolina Skagen:** Formal analysis, Methodology, Writing – review & editing. **Thor Håkon Skattør:** Formal analysis, Methodology, Writing – review & editing. **Mona Skjelland:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Markus KH Wiedmann:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

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