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Haemorrhagic intracranial complications associated with vaccine-induced thrombocytopenia or central venous thrombosis after COVID-19 vaccination: postulated underlying mechanisms with literature and case review

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ABSTRACT

Despite the unequivocal medical and social advantages of introducing vaccines against the novel coronavirus SARS-CoV-2, there were also some concerns regarding possible post-vaccination adverse events. Most of these are mild. But in rare cases, severe neurological symptoms including ischaemic stroke, intracranial haemorrhage (ICH), cerebral venous and sinus thrombosis (CVT), and thrombosis with thrombocytopenia (TTS) have been observed.

Literature data suggests that thrombosis with thrombocytopenia was the major underlying cause of the ICH; dural venous sinuses / cerebral veins were indicated as the primarily affected sites of thrombosis. Our review confirms the previously documented suspicion that CVT and TTS are most likely to occur following vector-type, rather than mRNA, vaccine administration. The postulated mechanism of TTS is similar to heparin-induced thrombocytopenia (HIT) both clinically and serologically. Although ICH and VITT are very rare side effects of the COVID-19 vaccine, for patients with risk factors for thrombosis (e.g. pregnancy), physicians should carefully consider the benefit/risk ratio of vaccination.

Keywords: SARS-CoV-2, COVID-19, vaccines, haemorrhagic stroke, sinus thrombosis

Introduction

Coronavirus Disease 2019 (COVID-19) has resulted in the deaths of more than 6 million people [1]. In order to reduce mortality and other complications associated with COVID-19 virus infection, several vaccines have been approved worldwide. Despite the obvious benefits of the COVID-19 vaccine, there have also been concerns about its adverse effects. In the majority of cases, adverse reactions to the most common vaccines including mRNA vaccines such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273, and vector vaccines such as ChAdOx1 nCOV-19, are mild [2–4]. These include headaches, fever, muscle and joint pain, chills, malaise, swelling and redness at the site of injection [5]. In rare cases, severe neurological syndromes including ischaemic stroke, intracranial haemorrhage (ICH), cerebral venous and sinus

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thrombosis (CVT), and thrombosis with thrombocytopenia (TTS) have been observed [6–8].

Considering the fact that manufacturers do not provide conclusive statistics, and the available statistics come from observational, non-commercial studies (focused mainly on CVT or TTS), in this paper we wanted to consider the state of knowledge regarding the abovementioned rare complications, their outcome, the type of patients, and the proposed mechanism of origin [9, 10].

There are several types of vaccine currently approved by the European Medicines Agency. The mRNA based vaccines include BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), while the adenoviral vector vaccines include ChAdOx1 nCov-19(AstraZeneca) and Ad26.COV.2.S (Janssen) [11]. All these vaccines immunise the organism against the SARS-CoV-2 spike protein by producing it *in vivo*, but via different mechanisms [12]. The mRNA vaccine uses antigen-encoding messenger RNA (mRNA) to cause transient expression of antigens once delivered to the cell in stabilised and encapsulated form. Expressed antigens are then recognised by the immune system, inducing both humoral and cellular responses [13, 14]. Viral vector vaccines stimulate the immune response by using modified, unrelated viruses as vectors to deliver antigen-coding genes into the host cell [13]. There is also one whole inactivated virus vaccine VLA2001, VLA2101 (Valneva) [11] and one recombinant protein-based nanoparticle vaccine NVX-CoV2373 (Novavax) which use recombinant parts of pathogenic proteins to stimulate the immune system [11, 13, 15].

The most common postulated direct mechanism of haemorrhagic complications after COVID-19 vaccine administration is due to vaccine-induced immune thrombotic thrombocytopenia (VITT). VITT in pathogenesis is similar to autoimmune heparin-induced thrombocytopenia (aHIT). This phenomenon is characterised by the presence of anti-platelet factor 4 (anit-PF4) as well as anti-heparin antibodies in the blood. These antibodies cross-link with FcγRIIA receptor on platelet, monocytes and neutrophils and initiate a process that leads to thrombocytopenia and a thrombotic state. Some studies have suggested that VITT is a clinical variant of HIT [16].

Another commonly described potential mechanism of haemorrhagic complications associated with SARS-CoV-2 is the induction of CVT based on the virus affinity to ACE2 receptors. The virus penetrates using the glycoprotein S (spike protein) and binds to the ACE2 receptors, which leads to damage of intracranial arteries, causing vessel wall rupture [17–20]. Binding of SARS-CoV-2 to the ACE receptors also results in angiotensin II elevation, which starts a process leading to a massive increase of inflammatory cytokines levels. This cytokine storm includes interleukin-1beta, interferon gamma, interferon-induced protein 10, monocytic chemoattractant protein 1 as well as IL-1, IL-2, IL-6, and tumour necrosis factor-alpha (TNF-alpha). This may not only result in endothelial dysfunction (which directly leads to ICH), but also cause microthrombosis and destabilisation of atherosclerotic plaques [21, 22, 17–20]. Since there have been cases of CVT with intracranial haemorrhage after COVID-19 vaccination, an analogous mechanism of origin should be considered [23–25].

Materials and method

Our review was based on a PubMed database search (MEDLINE) using the queries: 'COVID-19 Vaccines' [Mesh] AND 'Intracranial Haemorrhages' [Mesh]. 13 of the 17 records were further reviewed after they were found to be in accordance with the manuscript topic. The excluded studies were either in a language other than English, focused mainly on another topic, or the information provided was too brief and/or irrelevant to this review (Fig. 1).

Clinical presentation, prevalence, mortality

Pavord et al. performed a prospective cohort study involving patients with suspected vaccine-induced immune thrombocytopenia and thrombosis (VITT) in United Kingdom hospitals. Of 294 patients evaluated, 237 were suspected of

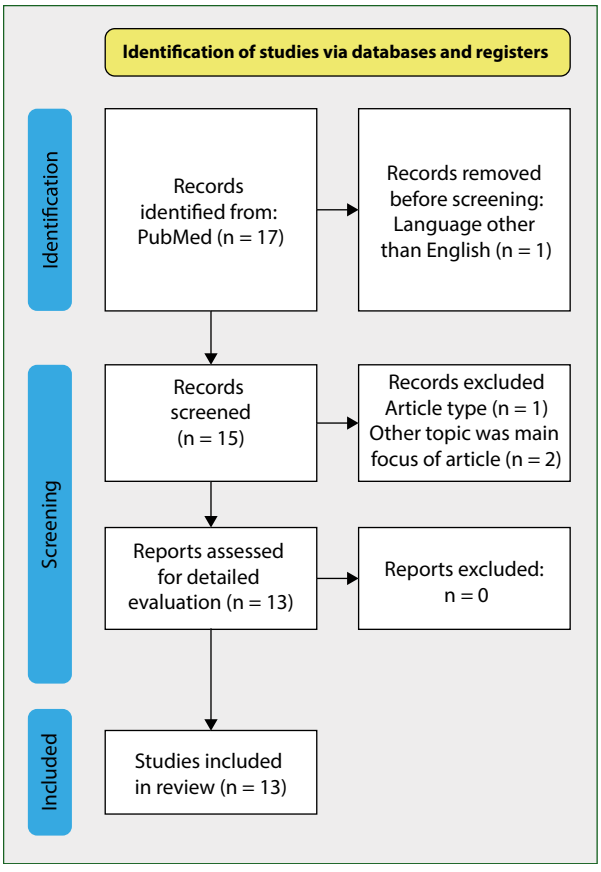

Figure 1. PRISMA chart of this study

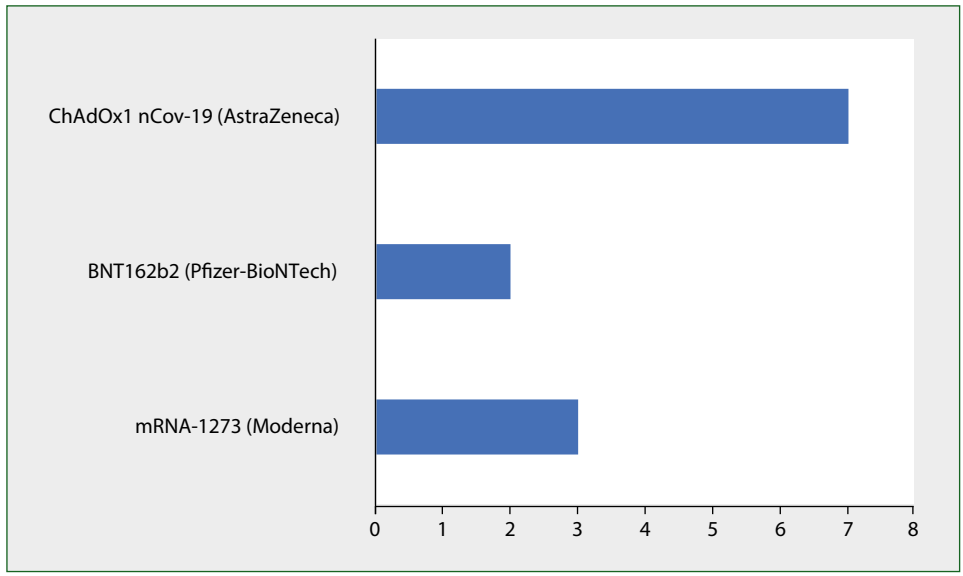

Figure 2. Comparison of number of intracranial haemorrhage complications in discussed cases with corresponding type of vaccine

VITT: 17 as having possible VITT, 50 as having probable VITT, and 170 as having definite VITT. All patients classified as probable or definite VITT were admitted after receiving the first dose of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine. The overall mortality rate was 22% (49 of 220 patients with definite or probable VITT), and patients with CVT, elevated d-dimer levels, and decreased fibrinogen levels were more likely to die. Anti-PF4 antibodies were present in 90% (198/220) of patients with definite or probable VITT. 50% of patients (110/220) had at least one CVT site, and 40% of these patients (36%) had CVT complicated by ICH. Thrombocytopenia was present in 95% of 217 patients with available platelet count data. The median time from vaccination to symptoms was 14 days (range 5–48) and median age was 48 years (range 18–79) [26].

Another clinical control study by Schulz et al. involved 45 cases of CVT in patients within one month of the first dose of COVID-19 vaccine in Germany. There were nine cases of ischaemic stroke, four of haemorrhagic stroke, and four of other neurological events. Of the 62 cases recorded, 85.5% of patients were vaccinated with the ChAdOx1 (AstraZeneca) vaccine and 14.5% with the BNT162b2 (Pfizer-BioNTech) vaccine; no cases were reported with the mRNA-1273 (Moderna) vaccine. Of the 45 cases of CVT, 37 were associated with ChAdOx1 and eight with BNT162b2. Among CVT patients, 77.8% were female and 80% were younger than 60 (median 43, range 20–89). The median time from last vaccine administration to the onset of neurological symptoms was nine days (range 1–25) in the CVT group. 28 (73.7%) patients out of the total 62 had a positive anti-PF4 antibody test as well as 22 (71%) in the CVT group. VITT was diagnosed in 25 patients (65.8%), including 20 with CVT (64.5%). In the CVT group, 26 (60.5%) had thrombocytopenia and 23 (69.7%) had elevated D-dimer levels. With the use of additional vaccination data from nine states in Germany, the authors estimated the incidence rate of CVT within one month of one dose to be 0.55 per 100,000 person-months (1.52 for ChAdOx1 and 0.11 for BNT1622b2) [8].

We also analysed 12 cases of ICH associated with COVID-19 vaccination. Detailed information as well as a comparison is set out in Supplementary Table 1. In most cases there was no relevant medical history. In two cases of female patients (Lin et al. and Mendes-de-Almeida et al.), there was history of autoimmunological diseases.

Lin et al. described the case of a 40-year-old female patient with a history of Sjogren's Disease and autoimmune thyroiditis vaccinated with two doses of Moderna (mRNA-1237). Three days after vaccination with the second dose, the patient was admitted to A&E with severe headache, decreased level of consciousness, and tonic-clonic seizures [27]. Detailed information regarding the diagnostic process and treatment is set out in Supplementary Table 1. The patient was finally diagnosed with Moyamoya angiopathy (MMA) as the symptoms and disease course were typical for this illness [9, 10]. Moyamoya syndrome is a cerebrovascular condition of uncertain origin. It predisposes to internal carotid artery stenosis and stroke. Ischaemic stroke or transient ischaemic attack (TIA) are common in childhood and ICH is typical in adults in moyamoya [28]. In this case, we can assume that ICH occurred probably due to moyamoya angiopathy rather than the vaccination. However, due to the temporal connection between vaccine administration and initial symptoms, the hypothesis that a COVID-19 vaccine can trigger a cascade of symptoms leading to ICH should be taken into consideration.

A second case involving a patient with Hashimoto's thyroiditis was described by Mendes-de-Almeida et al. The woman had controlled hypothyroidism due to HT, with no other relevant medical history. The day after receiving the first

dose of the ChAdOx1 nCov-19 vaccine (AstraZeneca), she developed mild symptoms i.e. chills, tremors, and feeling cold. The following day, she reported a rash on her legs, abdomen, and back, which resolved spontaneously. The patient was also 23 weeks pregnant [29]. Detailed information on the diagnostic process and treatment are included in Supplementary Table 1.

There was also one case involving a patient with a heart disease history. Baba et al. presented the case of a 90-year old male patient who developed severe thrombocytopenia with ICH and duodenal bleeding after a BNT162b2 (Pfizer-BioNTech) vaccination. The patient had a history of hypertension, hyperlipidemia and myocardial infarction, but no history of excessive bleeding or thrombocytopenia. Seven days following the first dose of vaccination, the patient developed gastric distress as well as purpura on the arms and legs, and two days later (nine days after vaccination) was admitted to hospital due to impaired consciousness [30]. Detailed information regarding this case can be found in Supplementary Table 1.

Discussion and conclusions

Intracranial haemorrhage is a very rare complication after COVID-19 vaccination. In most of the cases described, the cause of ICH was thrombosis with thrombocytopenia with cerebral venous and/or sinus thrombosis as the original site of thrombosis [23–25, 29, 31, 32]. In a minority of cases, ICH occurred due to vascular disorders or vasculitis, and in each of these cases the patient was vaccinated with an mRNA vaccine [7, 27]. The postulated mechanism of TTS is similar to that of heparin-induced thrombocytopenia (HIT) both clinically and serologically [33]. Patients with vaccine-induced thrombocytopenia in most cases present a high level of anti PF4 antibodies, but unlike classic HIT present acute thrombocytopenia with a low level of fibrinogen and an elevated d-dimer level [34, 35].

The most commonly used COVID-19 vaccines, i.e. mRNA-based as well as adenoviral vector vaccines, target the SARS-CoV-2 spike protein [12]. Likewise, the most commonly postulated mechanism of ICH in the course of thrombosis involves binding of the spike protein to the ACE2 receptor [17–20].

Since the abovementioned vaccines stimulate cells to produce SARS-CoV-2 spike protein *in vivo* through different mechanisms, it can be assumed that in a particular group of patients with an unknown, independent risk factor, COVID-19 vaccination may be the direct cause of ICH; however, this statement requires further, in-depth, investigation.

ICH was present in the temporal lobe or temporoparietal/temporooccipital region on imaging studies in most cases (9/11). In one case, ICH was localised in the frontal lobe. In the majority of cases, the ICH area was surrounded by oedema, and four cases had coexisting SAH [7, 23–25, 27, 29–31, 36]. There was also one case of adenohypophysis haemorrhagic bleeding [37] and one case of left basal ganglia ICH [38]. In one case, acute haematoma in the cerebral falx was described coexisting with occipital small subarachnoid haemorrhage and left subcortical haemorrhage [30].

TTS/VITT after vaccination with vector-type vaccines such as ChAdOx1 nCov-19 (AstraZeneca) and Ad.26.COV2.s (Janssen) has been documented in the past [20–22]. Our review confirms that the prevalence of CVT and TTS is likely to be higher after vector-type vaccine injection (6 of 11 cases cited, > 80% in other studies). However, cases of deep vein thrombosis after administration of mRNA vaccine (e.g. Pfizer/BioNTech) have also been documented, which may also result in TTS [7, 24, 39]. In addition, higher occurrence rates of SAH were observed in studies after the third dose of mRNA vaccine [40] (Fig. 2).

Potentially significant co-morbidities were reported merely in three of the cases. Two cases, those described by Lin et al. and Mendes-de-Almeida et al., involved autoimmune diseases, autoimmune thyroiditis and Sjogren's Disease respectively [27, 29]. Since the most commonly postulated mechanism of ICH after COVID-19 vaccination is VITT, this could lead to an assumption that patients with other autoimmune diseases are at higher risk of developing VITT. However, in the first case (Lin et al.), the patient was eventually diagnosed with Moyamoya angiopathy that was more likely to be the cause of ICH [27]. Given that links between autoimmune diseases and COVID-19 vaccination have been observed in the past [41, 42], possible associations between VITT and autoimmune disorders require further investigation. In the case reported by Mendes-de-Almeida et al., the patient was 23 weeks pregnant, which could also be an independent risk factor [29]. In a single case, COVID-19 vaccination was administered in a patient with a history of cardiovascular diseases, i.e. hypertension, hyperlipidemia and myocardial infarctions. These are well-established risk factors of ICH, and together with VITT and potential endothelium impairment due to ACE-2 receptor involvement, might prompt the risk of post-vaccination ICH. However, further research and analysis is necessary to understand a potential connection between VITT and ACE-2-related endothelial damage, and the increased the risk of post-vaccination ICH [17–20].

Considering the fact that one of the most frequently mentioned causes of ICH is CVT, it is likely that there are potential independent risk factors for both of these phenomena, apart from COVID-19 vaccination. In one case there was Sjogren's Disease, which could be a CVT risk factor on its own, but in this case, the most likely cause of ICH (directly) was Moyamoya disease [28, 43]. As mentioned above, in one case there were also direct vascular risk factors of ICH, which may also be CVT risk factors individually, as well as with often coexisting obesity, which may also increase CVT risk [30, 43–45]. In addition, in one of the cases described, there was diabetes mellitus, which alone, or in combination with other vascular risk factors, can impair the function of small intracranial arteries leading directly to ICH, as well as being one of

the indirect CVT risk factors [24, 43, 44, 46]. However, given that the comorbidities described above only occurred in two separate cases, determining the extent to which the described risk factors translate into ICH in the short term following COVID-19 vaccination requires further investigation.

Although ICH and VITT are very rare adverse reactions to COVID-19 vaccination, the presence of persistent or recurrent headache within 30 days after vaccination, especially with the vector-type vaccines (AstraZeneca and Janssen), should provoke suspicion [29, 47]. In cases of patients with thrombosis risk factors such as pregnancy, physicians should carefully consider the vaccination risk/benefit [29].

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