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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Neuroradiology

Retrospective review COVID-19 vaccine induced thrombotic thrombocytopenia and cerebral venous thrombosis-what can we learn from the immune response

Ana M. Franceschi a,*, David R. Petrover a, Timothy M. McMahon a, Richard B. Libman b, Luca Giliberto b, Sean A.P. Clouston c, Mauricio Castillo d, Claudia Kirsch e, f, g

a Neuroradiology Section, Department of Radiology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, Manhasset, NY, USA
b Institute for Neurology and Neurosurgery, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, Manhasset, NY, USA
c Department of Family, Population and Preventive Medicine and Program in Public Health, Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, USA
d Neuroradiology Section, Department of Radiology, University of North Carolina School of Medicine, Chapel Hill, NC, USA
e Yale Department of Radiology and Biological Imaging, New Haven, CT, USA
f PhD Candidate for Viral Mediated Disease in the Skull Base, The School of Clinical Dentistry, University of Sheffield, Sheffield, UK
g Adjunct Professor Diagnostic, Molecular and Interventional Radiology Biomedical Engineering Imaging Mount Sinai Hospital, New York, NY, USA

ARTICLE INFO
Keywords:
Cerebral venous thrombosis(CVT)
CT and MR venography
SARS-CoV-2
COVID-19
Vaccine induced immune thrombotic thrombocytopenia (VITT)
Adenoviral vector vaccine
Platelet factor 4 (PF4) cytokine

ABSTRACT

Introduction: Cerebral Venous Thrombosis (CVT), prior to the COVID pandemic, was rare representing 0.5 of all strokes, with the diagnosis made by MRI or CT venography.1–3 COVID-19 patients compared to general populations have a 30–60 times greater risk of CVT compared to non-affected populations, and up to a third of severe COVID patients may have thrombotic complications.4–8 Currently, vaccines are the best way to prevent severe COVID-19. In February 2021, reports of CVT and Vaccine-induced immune thrombotic thrombocytopenia (VITT) related to adenovirus viral vector vaccines including the Oxford-AstraZeneca vaccine (AZD1222 (ChAdOx1)) and Johnson & Johnson COVID-19 vaccine (JNJ-78436735 (Ad26.COV2-S)), were noted, with a 1/583,000 incidence from Johnson and Johnson vaccine in the United States.11, 12 This study retrospectively analyzed CVT and cross-sectional venography at an Eastern Medical Center from 2018 to 2021, and presents radiographic examples of CVT and what is learned from the immune response.

Methods: After IRB approval, a retrospective review of cross-sectional CVT and MRVs from January 1st 2018 to April 30th 2021, at a single health system was performed. Indications, vaccine status, patient age, sex, and positive finding incidence were specifically assessed during March and April for each year. A multivariable-adjusted trends analysis using Poisson regression estimated venogram frequencies and multivariable logistic regression compared sex, age, indications and vaccination status.

Results and discussion: From January 1, 2018 to April 30, 2021, (Fig. 1), a total of n = 2206 in patient and emergency room cross-sectional venograms were obtained, with 322 CVTs and 1884 MRVs. In 2018, 2019, 2020, respective totals of cross-sectional venograms were 568, 657, 660, compared to 321 cross-sectional venograms in the first four months of 2021. CVT in 2018, 2019, 2020, respective totals were 51, 86, 97, MRV totals were 517, 571, 563, compared to the 2021 first four month totals of 88 CVTs and 233 MRVs. March, April 2018, 2019, 2020, CVTs respectively were 6, 17, 11, compared to the 2021 first four months of 59 CVTs, comprising 63% of the total 93 CVTs, respective MRVs were 79, 97, 52, compared to 143 MRVs in the first four months of 2021 for 39% of the total 371 MRVs. In March, April 2020 during the pandemic onset, cross-sectional imaging at the East Coast Medical Center decreased, as priorities were on maintaining patient ventilation, high level of care and limiting spread of disease. In March/April 2021, reports of VITT and CVT likely contributed to increased CTVs and MRVs, of 39.65% [1.20–1.63] increase (P < 0.001) from prior. In March, April 2021 of 202 venograms obtained, 158 (78.2%) were unvaccinated patients, 16 positive for CVT (10.1%), 44 were on vaccinated patients (21.7%), 8 specifically ordered with vaccination as a clinical indication, 2 positive for CVT (4.5%), (odds ratio = 0.52 [0.12–2.38], p = 0.200).

* Corresponding author at: Lenox Hill Hospital, Department of Radiology, 100 East 77th Street, 3rd Floor, New York, NY 10075, USA.
E-mail address: afranceschi@northwell.edu (A.M. Franceschi).

https://doi.org/10.1016/j.clinimag.2022.06.020
Received 18 February 2022; Received in revised form 20 June 2022; Accepted 28 June 2022
Available online 15 July 2022
0899-7071/© 2022 Elsevier Inc. All rights reserved.
Conclusion: CTV prior to the COVID pandemic, was rare, responsible for 0.5 of all strokes, at the onset of the pandemic in the East Coast, overall cross-sectional imaging volumes declined due to maintaining ventilation, high levels of care and limiting disease spread, although COVID-19 patients have a 30–60 times greater risk of CTV compared to the general population, and vaccination is currently the best option to mitigate severe disease. In early 2021, reports of adenoviral vector COVID vaccines causing CTV and VITT, led to at 39.65% increase in cross-sectional venography, however, in this study unvaccinated patients in 2021 had higher incidence of CTV (10.1%), compared to the vaccinated patients (4.5%). Clinicians should be aware that VITT CTV may present with a headache 5–30 days post-vaccination with thrombosis best diagnosed on CTV or MRV. If thrombosis is present with thrombocytopenia, platelets <150 × 10^9, elevated D-Dimer >4000 FEU, and positive anti-PF4 ELISA assay, the diagnosis is definitive. VITT CTV resembles spontaneous autoimmune heparin induced thrombocytopenia (HIT), and is postulated to occur from platelet factor 4 (PF4) binding to vaccine adenoviral vectors forming a novel antigen, anti-PF4 memory B-cells and anti-PF4 (VITT) antibodies.

1. Introduction

Cerebral Venous Thrombosis (CTV), involves clot formation in dural sinuses, deep or cortical veins. Prior the COVID-19 pandemic, CTV was associated with 0.5% of strokes, with a rare incidence of 3–4 cases per one million adults, and slightly higher incidence of 7 cases per one million in pediatric patients. Risk factors for CTV include congenital or acquired hematologic abnormalities, oral contraceptives, cancer, trauma, infection, inflammatory diseases or dehydration. CTV most commonly presents with headache, because initial exams may non-contributory, early accurate cross-sectional CT or MRI diagnosis is critical to prevent. Progression to intracerebral infarction and hemorrhage with high morbidity and mortality. Since December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 virus (SARS-CoV-2) causing the COVID-19 pandemic, has resulted in 6.26 million deaths and 521 million infections worldwide. Severe COVID-19, may cause respiratory distress, thrombotic myocardial events, strokes or CTV in up to a third of patients, with a 30–60 time greater risk for CTV versus unaffected populations. To mitigate severe COVID-19 infections, mRNA vaccines were rapidly developed and first administered December 2020 in the United States. In February 2021, CTV with a thrombotic thrombocytopenia after adenoviral vector administration was reported. The Centers for Disease Control (CDC) and FDA recommended discontinuing the Janssen/Johnson & Johnson vaccine on April 13th 2021. On May 5, 2022, the FDA limited the authorized use of the Janssen COVID-19 vaccine because of “the risk of thrombosis with thrombocytopenia syndrome (TTS)”.

Why adenoviral vector COVID-19 vaccines cause CTV VITT, is unknown. It is postulated the adenoviral binding to platelet factor 4 (PF4) a positive cytokine, forms a novel antigen, resulting in anti-PF4 memory B-cells and anti-PF4 (VITT) antibodies.

This study retrospectively assessed CT and MRI venography, from January 1, 2018 to April 30, 2021, at a single health system, prior to and during the initial COVID pandemic and COVID-19 vaccination reporting of CTV VITT. Cross-sectional venography studies were analyzed comparing, utilization, indications, vaccination status, age, sex, and modalities with multivariable-adjusted trends analysis using Poisson regression estimated venogram frequencies and multivariable logistic regression. CTV radiographic findings, modalities for diagnosis and potential etiologies for how adenoviral vector vaccines lead to CTV are illustrated.

2. Methods

2.1. Ethics

Institutional review board approval (IRB 21-0533), was obtained. The IRB waived the need for written informed consent due to the retrospective nature of the study.

Total numbers of inpatient and emergency department cerebral
computed tomography venograms (CTVs) and magnetic resonance venograms (MRVs) acquired from January 1st, 2018 to April 30th, 2021 from a single health system were retrospectively reviewed. Retrospective analysis included number of studies and modality obtained Magnetic Resonance Venography (MRV) or Computed Tomography Venography (CTV), patient age, sex, vaccination status, incidence of CVT for each consecutive year from 2018 to 2021. Total numbers of CTVs, MRVs, and intracranial venous thrombosis prevalence in the months of March and April, pre COVID pandemic in 2018, 2019, early COVID-19 pandemic March, April 2020, and at the initiation of COVID vaccination in March, April 2021 with reporting of CVT VITT from COVID-19 adenoviral vector vaccines.

2.2. Statistical analysis

The modality CTV and MRV order rates were analyzed separately. A multivariable-adjusted trends analysis using Poisson regression estimated increases in cerebral venogram usage rate in March and April.
Fig. 4. MRI 3D T1 MPRAGE post gadolinium contrast A) axial, B) sagittal, C) coronal, central absent enhancement right transverse and sigmoid sinuses (yellow arrows), and proximal right internal jugular vein (blue arrow), with no intracranial hemorrhage or infarction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
2021 during the vaccination period, with order frequencies provided for March, April in 2018, 2019, and 2020 separately. Demographic pattern differences for ordering venograms were delineated and increases in ordering were reported and stratified by imaging modality (MRV versus CTV). The role of vaccination in venogram ordering was assessed using multivariable logistic regression and compared to venogram status by participant sex and vaccination status in March, April 2021 (Fig. 1).

3. Results

As in Fig. 1, from January 1st, 2018 to April 30th, 2021, a total of 2206 cerebral venograms were obtained (CTV = 322, MRV = 1884). In 2018, 2019, 2020, respective totals of cross-sectional venograms were 568, 657, 660, compared to 321 cross-sectional venograms in the first four months of 2021. Total CTVs in 2018, 2019, 2020, were 51, 86, 97, MRV totals were 517, 571, 563, compared to the 2021 first four month totals of 88 CTVs and 233 MRVs. In March, April 2018, 2019, 2020, CTVs respectively were 6, 17, 11, compared to the 2021 first four months of 59 CTVs, comprising 63% of the total 93 CTVs from January 2018 – April 2021. In March, April 2018, 2019, 2020, respective MRVs were 79, 97, 52, compared to 143 MRVs in the first four months of 2021 for 39% of the total 371 MRVs from January 2018 to April 2021. The total yearly number of venograms in 2019 was 657, with only a minimal increase from 657 in 2019 to 660 in 2020. Of note, is the decreased number of venograms in March, April 2020, compared to prior years with only 11 CTVs and 52 MRVs, for a total of 63 cross-sectional venograms, a 55% reduction compared to 2019. March and April 2020 coincide with the COVID pandemic onset in the Eastern United States, with a large influx COVID-19 patients admitted in respiratory distress requiring urgent ventilation, declines in cross-sectional including venography likely reflect a focus on handling the influx of COVID patients requiring ventilation and high level care as well as minimizing patient transport and infectious exposure.

In March, April 2021, reports of CVT VITT after COVID-19 adenovector viral vaccines, likely contributed to increased volumes of CTVs and MRVs, with a 39.65% increased volume of venograms [1.20–1.63] (P < 0.001) compared to decreased cross-sectional volumes at the COVID pandemic onset in 2020, and pre-pandemic studies in 2018 and 2019.

In March, April 2021 of 202 venograms obtained, 158 (78.2%) were on unvaccinated patients, of which 16 were positive for CVT (10.1%), 44 were on vaccinated patients (21.7%), 8 specifically ordered with vaccination as a clinical indication, only 2 positive for CVT (4.5%), (odds ratio = 0.52 [0.12–2.38], p = 0.200). There were no significant differences in female to male ratios or patient’s average age receiving venograms in March/April-2021 (p = 0.163). The overall mean percent increase of venogram volumes in March/April 2021 was 622% for CTV and 221% for MRV, compared to 2018–2020. [Fig. 1].

4. Discussion

Initial clinical exam findings in CVT may non-specific such as headache, making an accurate early radiographic diagnosis critical, because progression of CVT can result in seizures, encephalopathy, altered consciousness, infarct, hemorrhage, and focal neurologic deficits with resultant morbidity and mortality, CTV or MRV may demonstrate dural sinus thrombosis (ST) most commonly the superior sagittal sinus, followed by the transverse sinus. In approximately 10% of ST, the clot can propagate to deep central veins such as the vein of Galen or paired internal cerebral veins, or into the cortical veins.

Radiographic features of CVT include high density thrombotic clot in the venous system on noncontrast CT (Fig. 2). On non-contrast MRI, thrombus may have intrinsic T1 iso or hyperintensity, on both contrast CT and MR with a contrast filling defect (Figs. 3-5). Brain parenchyma along a sinus thrombosis may have edema that does not follow arterial borders, infarction, subarachnoid or intraparenchymal hemorrhage. Deep venous thrombosis may result in bilateral thalami and lentiform nuclei edema or infarcts.

Cross-sectional CT or MR venography both have a high sensitivity and specificity for diagnosing CVT. Advantages of CT include its ease of availability, rapid scan times, and absence of e pre-screening. Disadvantages of CT include ionizing radiation exposure. MRI, provides superior soft tissue visualization, and can be performed without contrast and ionizing radiation. Limitations for MRI include safety considerations.
Fig. 6. PF4, CXC cytokine is by platelet activation in granules and induces neutrophil migration. Electropositive PF4 (blue dots) is attracted to electronegative adenovirus capsid, possibly forming novel antigen that monocytes take to lymph nodes leading to B-cell stimulation and anti-PF4 memory B-cells and anti-PF4 (VITT) antibodies.

Anti-PF4 antibodies increase platelet activation and fibrinogen production stimulating more PF4 granules to be released inducing neutrophil extracellular traps, increasing active tissue factor seen in thrombogenesis.

Platelets continually attack & reactivate fibrinogen D-dimer increase, central venous thrombogenesis associated with increased active tissue factor associated with fibrinogen & active tissue factor increase associated with VITT trap platelets increasing clotting.
for metallic hardware that may be affected by magnetic fields, such as a cardiac pacemaker, therefore requiring pre-screening. In addition, critically ill patients, monitoring requires MRI compatible equipment, and the need for patients to hold still with longer scan times.

In March and April 2020 the Eastern United States, experienced a marked increased number of COVID-19 patients hospital admissions often requiring urgent respiratory assistance, during this time there was a converse decline in cross-sectional venography likely from a focus on maintaining COVID patients on ventilators requiring high level care and minimizing transport to radiology and infectious exposure.

In December 2020 to March 2021, the United States Federal Drug Administration (FDA) granted Emergency Use Authorization (EUA) to three vaccines including two messenger RNA-based vaccines — BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) encoding the spike protein antigen of SARS-CoV-2, encapsulated in lipid nanoparticles and Ad26.COV2-S (Johnson & Johnson/Janssen), and a recombinant adenoivirus type 26 vector vaccine encoding SARS-CoV-2 spike glycoprotein. In Europe, the Medicines Agency (EMA) granted approval for the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine, a recombinant chimpanzee adenoavirus vector encoding the spike glycoprotein of SARS-CoV-2.

In Europe, CVT thrombotic events with thrombocytopenia were observed following AstraZeneca vaccine administration. In Norway, 5 cases of unusual venous thromboembolism, were reported occurring 7–10 days post AstraZeneca vaccination in 4 females age 37–54, all with CVTs, and a 32 year old asthmatic male with portal, hepatic, splenic and basivertebral venous thrombosis. All patients had elevated antibodies to platelet factor 4–polyanion complexes and no prior heparin exposure, 3 female patients had severe CVT, intracranial hemorrhages and fatal outcomes, one female and one male patient survived. In Germany and Austria, Greinacher et al. described 11 patients with similar thrombosis and thrombocytopenia syndrome following AstraZeneca vaccination. All patients had severe CVT, one patient presented with fatal intracranial hemorrhage, likely from CVT VITT. Initial UK Medicine and Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency (EMA), responses were “there is no evidence that blood clots in veins are occurring more than would be expected.” The following week, the cases and research information was circulated on platforms such as Twitter, with Norway, Germany and the United Kingdom, reports on CVT after Oxford-AstraZeneca vaccine administration with thrombocytopenia and antiplatelet factor 4 (anti-PF4) antibodies, termed Vaccine-induced immune thrombocytopenia (VITT). The mechanism causing CVT VITT, resembles heparin-induced thrombocytopenia (HIT), a prothrombotic disorder caused by platelet-activating antibodies recognizing multimolecular complexes between cationic platelet factor 4 (PF4) and anionic heparin. It is postulated the adenoaviral binding to platelet factor 4 (PF4) a positive cytokine, forms a novel antigen, in turn may taken up by monocytes and brought to lymph nodes, resulting in anti-PF4 memory B-cells and anti-PF4 (VITT) antibodies.

The elevated levels of antibodies to platelet factor 4–polyanion complexes in CVT VITT, lead to computation analysis of the adenoaviral ChAdOx1 viral vector capsid and receptor binding fiber knob protein interactions with CD46, coxsackie and adenovirus receptor (CAR), and the PF4 cytokine. The models revealed PF4 (platelet factor 4) a cytokine that induces neutrophil migration, and CXC cytokine with 2 N-terminal cysteines separated by an amino acid, has an electropositive charge complementary to the adenoaviral ChAdOx1 viral capsid surface electronegative charge, with PF4 binding the viral capsid, with a shape allowing it enter in between viral hexons. The novel antigen, taken up by monocytes and resulting in anti-PF4 memory B-cells and anti-PF4 (VITT) antibodies, creates a viscous loop of platelet reactivation with release of PF4 cytokines.

5. Conclusion

Patients with COVID-19 compared to unaffected populations have a 30 to 60 times increased risk of cerebral venous thrombosis (CVT) and up to a third of patients with severe COVID may have thrombotic complications. Currently, vaccination is the best countermeasure in preventing severe COVID-19. In February of 2021 reports of CVT and VITT from adenoaviral vector vaccines including the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine, a recombinant chimpanzee adenoavirus vector encoding the spike glycoprotein of SARS-CoV-2 and Ad26. COV2-S (Johnson & Johnson/Janssen), a recombinant adenovirus type 26 vector encoding SARS-CoV-2 spike glycoprotein were noted. CVT VITT usually occurred 5 to 10 days after vaccination, predominantly in female patients under the age of 60, with a 40% mortality, leading to interim considerations and that the vaccines had to indicate that women aged 18 to 49 years should be aware of the increased risk of CVST with thrombocytopenia following receipt of vaccination. The public and medical awareness, likely lead to increased ordering of venograms as noted in March/April 2021, compared to the previous years. Interestingly the majority 158 (78.2%) were on unvaccinated patients, and 16 were positive for CVT (10.1%), of the 44 performed on vaccinated patients (21.7%), 8 were specifically ordered with vaccination as a clinical indication, with 2 positive for CVT (4.5%), (odds ratio = 0.52 [0.12–2.38], p = 0.200). Although, CVT VITT is rare, awareness that headache may be a presenting sign and patients may need CTV or MRV 10 days after vaccine administration, may be necessary to exclude CVT VITT.

None.

Declaration of competing interest

None.
References

1. Ropper AH, Klein JP. Cerebral venous thrombosis. N Engl J Med 2021 Jul 1;385(1):59-64. https://doi.org/10.1056/NEJMra2106545. PMID: 34192432.

2. Aliprandi A, Borrelli P, Polonia V, Salmaggi A. Headache in cerebral venous thrombosis. Neurosurgery 2020 Dec 41(Suppl 2):401-6. https://doi.org/10.1093/neuros/nyaa347.

3. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol 2007 Feb;6(2):162-70. https://doi.org/10.1016/S1474-4422(07)70029-7. PMID: 17239803.

4. Weekly epidemiological update on COVID-19. World Health Organization. URL: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—25-january-2022. [Accessed 23 January 2022].

5. Greinacher A, Selleng K, Schlaudraff P, et al. Insights in ChAdOx1 nCoV-19 vaccine-induced thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2124-30. https://doi.org/10.1056/NEJMoa2108480. Epub 2021 Apr 9. PMID: 33835769; PMCID: PMC8095372.

6. Rizk JG, Gupta A, Sardar P, Henry BM, Lewin JC, Lippi G, Lavie CJ. Clinical features of vaccine induced immune thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2022-11. https://doi.org/10.1056/NEJMoa2108480. Epub 2021 Apr 9. PMID: 33835769; PMCID: PMC8095372.

7. Klein DE, Libman R, Kirsch C, Arora R. Cerebral venous thrombosis: a typical presentation of COVID-19 in the young. J Stroke Cerebrovas Dis 2020 Aug 29(8):104989. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104989.

8. Siegler JE, Cardona P, Arenillas JF, Talavera B, Guillen AN, Chavarra-Miranda A, de Benito-Levid-19—25-january-2022. [Accessed 23 January 2022].

9. Ropper AH, Klein JP. Cerebral venous thrombosis. N Engl J Med 2021 Jul 1;385(1):59-64. https://doi.org/10.1056/NEJMra2106545. PMID: 34192432.

10. Feldman PA. Proposed mechanism for rare thrombotic events after use of some COVID-19 vaccines. JAMA 2021;325:2448-56. https://doi.org/10.1001/jama.2021.2448.

11. Blazkova J, Skalicky P, Bradac O, Benes Jr V. Cerebral venous sinus thrombosis in COVID-19 patients: a multicenter study and review of literature. Accepted January 23rd, May 5, 2022. URL: J Stroke Cerebrovas Dis 2021; 30:105733. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.

12. Feldman PA. Proposed mechanism for rare thrombotic events after use of some COVID-19 vaccines. JAMA 2021;325:2448-56. https://doi.org/10.1001/jama.2021.2448.

13. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Azhar S. Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. J Neuroinflammation 2020 Aug 6;17(1):231. https://doi.org/10.1186/s12974-020-01896-9.

14. Pavord S, Scully M, Hunt BJ, et al. Clinical features of vaccine induced immune thrombotic thrombocytopenia with cerebral venous sinus thrombosis in COVID-19 patients. Med Hypotheses 2022 Jan;3:110756. https://doi.org/10.1016/j.mehy.2021.110756.

15. Ellis RM, Breuer T, Hauck K, et al. Vaccine induced immune thrombotic thrombocytopenia (VITT) with implications for thrombosis with thrombocytopenia syndrome among vaccine recipient, United States, April 2021. MMWR Morb Mortal Wkly Rep. 2021. Epub Aug 29 PMID: 34192432.

16. Blazkova J, Skalicky P, Bradac O, Benes Jr V. Cerebral venous sinus thrombosis in COVID-19 patients: a multicenter study and review of literature. Accepted January 23rd, May 5, 2022. URL: J Stroke Cerebrovas Dis 2021; 30:105733. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.

17. Feldman PA. Proposed mechanism for rare thrombotic events after use of some COVID-19 vaccines. JAMA 2021;325:2448-56. https://doi.org/10.1001/jama.2021.2448.

18. Feldman PA. Proposed mechanism for rare thrombotic events after use of some COVID-19 vaccines. Med Hypotheses 2022 Jan;3:110756. https://doi.org/10.1016/j.mehy.2021.110756.

19. Greinacher A, Selleng K, Palanhar R. Insights in ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia (VITT). Blood. 2021. https://doi.org/10.1182/blood.2021013231. published online Sept 29.

20. Bäker AT, Boyd RJ, Sarkar D, et al. The structure of ChAdOx1/Ad2222 reveals interactions with CAR and PF4 with implications for vaccine-induced immune thrombotic thrombocytopenia. bioRxiv. 2021. https://doi.org/10.1101/2021.05.19.444882. pub 5/24.

21. Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. Lancet Haematol 2022 Jan;9(1):e73–80. https://doi.org/10.1016/S2352-3026(21)00085-9.

22. Rabin JA, Taniguchi DM, Kacerovsky K, et al. COVID-19 vaccine—summary of Yellow Card. https://tinyurl.com/uyw7visq (accessed Jan29,2022).

23. Claps AM, Franceschi et al. Clinical Imaging 90 (2022) 63–70. Clinical Imaging 90 (2022) 63–70. https://doi.org/10.1016/j.clinimag.2021.02.024.