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Neuroradiology



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

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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.COVS-2)), 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 CTV 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 CTVs 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. CTV 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 CTVs and 233 MRVs. 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, 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).

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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 CVT 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 a 39.65% increase in cross-sectional venography, however, in this study unvaccinated patients in 2021 had higher incidence of CVT (10.1%), compared to the vaccinated patients (4.5%). Clinicians should be aware that VITT CVT 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 $<150 \times 10^9$, elevated D-Dimer >4000 FEU, and positive anti-PF4 ELISA assay, the diagnosis is definitive.¹³ VITT CVT 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.^{14–17}

1. Introduction

Cerebral Venous Thrombosis (CVT), involves clot formation in dural sinuses, deep or cortical veins. Prior the COVID-19 pandemic, CVT 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.¹ Risk factors for CVT 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.^{2,3}

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.⁴ Severe COVID-19, may cause respiratory distress, thrombotic myocardial events, strokes or CVT in up to a third of patients, with a 30–60 time greater risk for CVT versus unaffected populations.^{5–11} To mitigate severe COVID-19 infections, mRNA vaccines were rapidly developed and first administered December 2020 in the United States.

In February 2021, CVT with a thrombotic thrombocytopenia after adenoviral vector administration was reported.^{12–16} The Centers for Disease Control (CDC) and FDA recommended discontinuing the Janssen/Johnson & Johnson vaccine on April 13th 2021.^{12–16} 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 CVT 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.^{15,17–22}

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 CVT 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 CVT 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

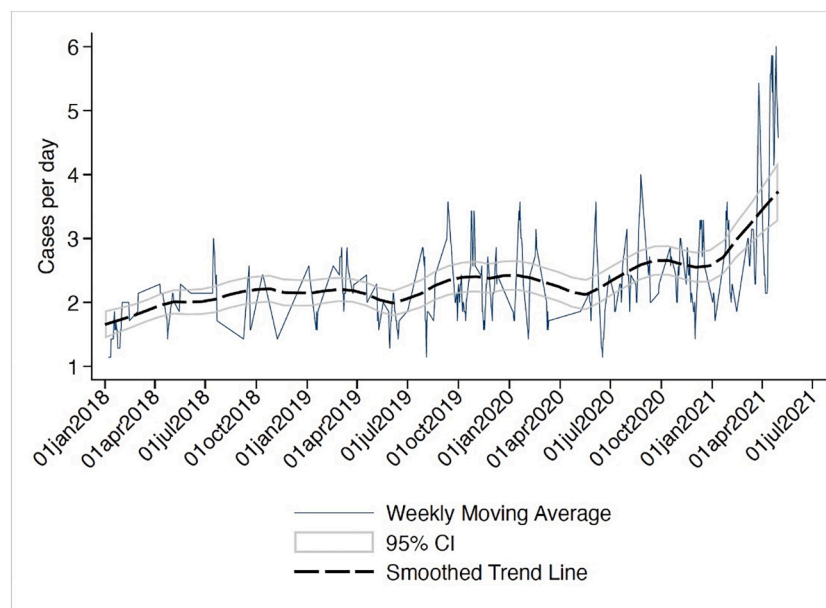


Fig. 1. Cerebral venogram CTV and MRV totals, January 1, 2018, to April 30, 2022.

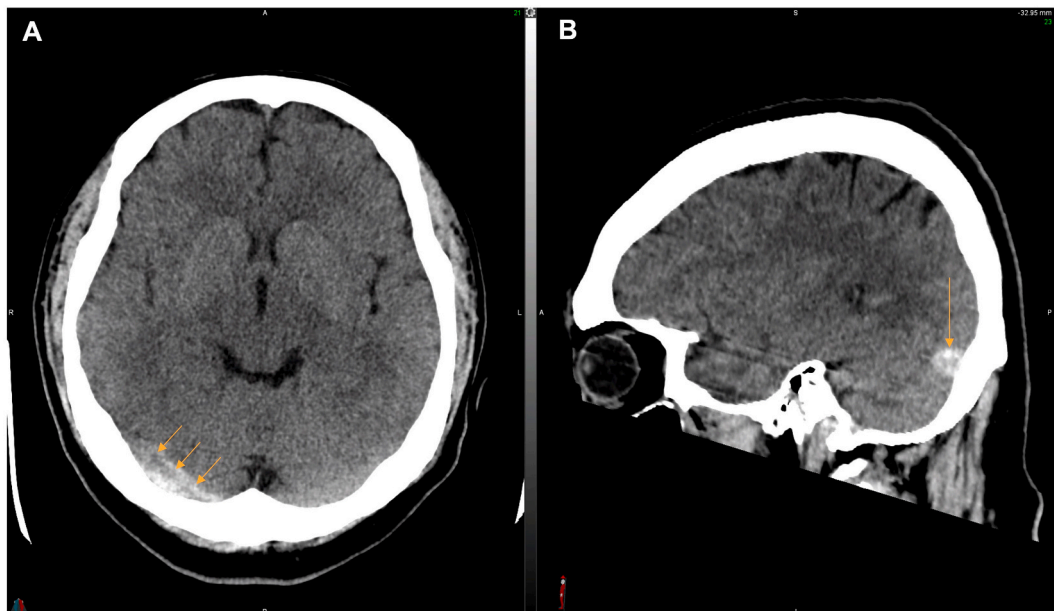


Fig. 2. Non-contrast A) axial, B) sagittal head CT with focal high attenuation cerebral venous sinus thrombosis in right transverse and right sigmoid sinuses (orange arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

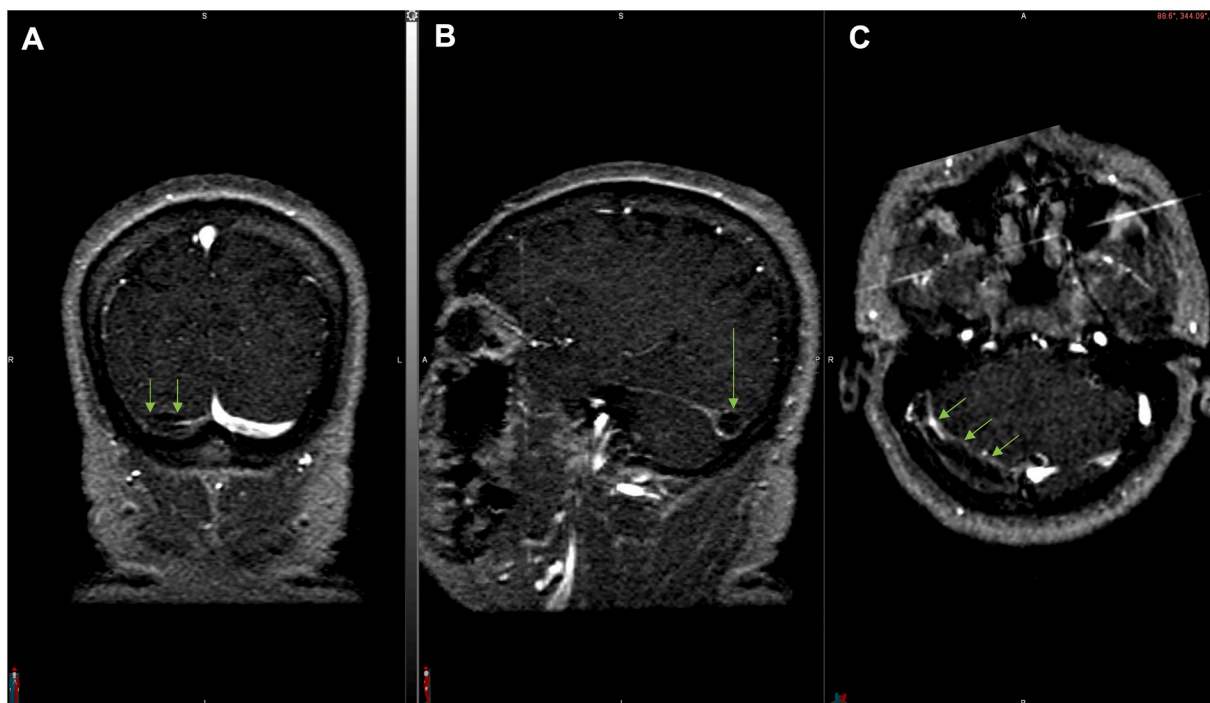


Fig. 3. MR venogram A) coronal, B) sagittal and C) axial 2D time-of-flight with loss of flow-related signal right transverse and sigmoid sinuses (green arrows), confirming cerebral venous sinus thrombosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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

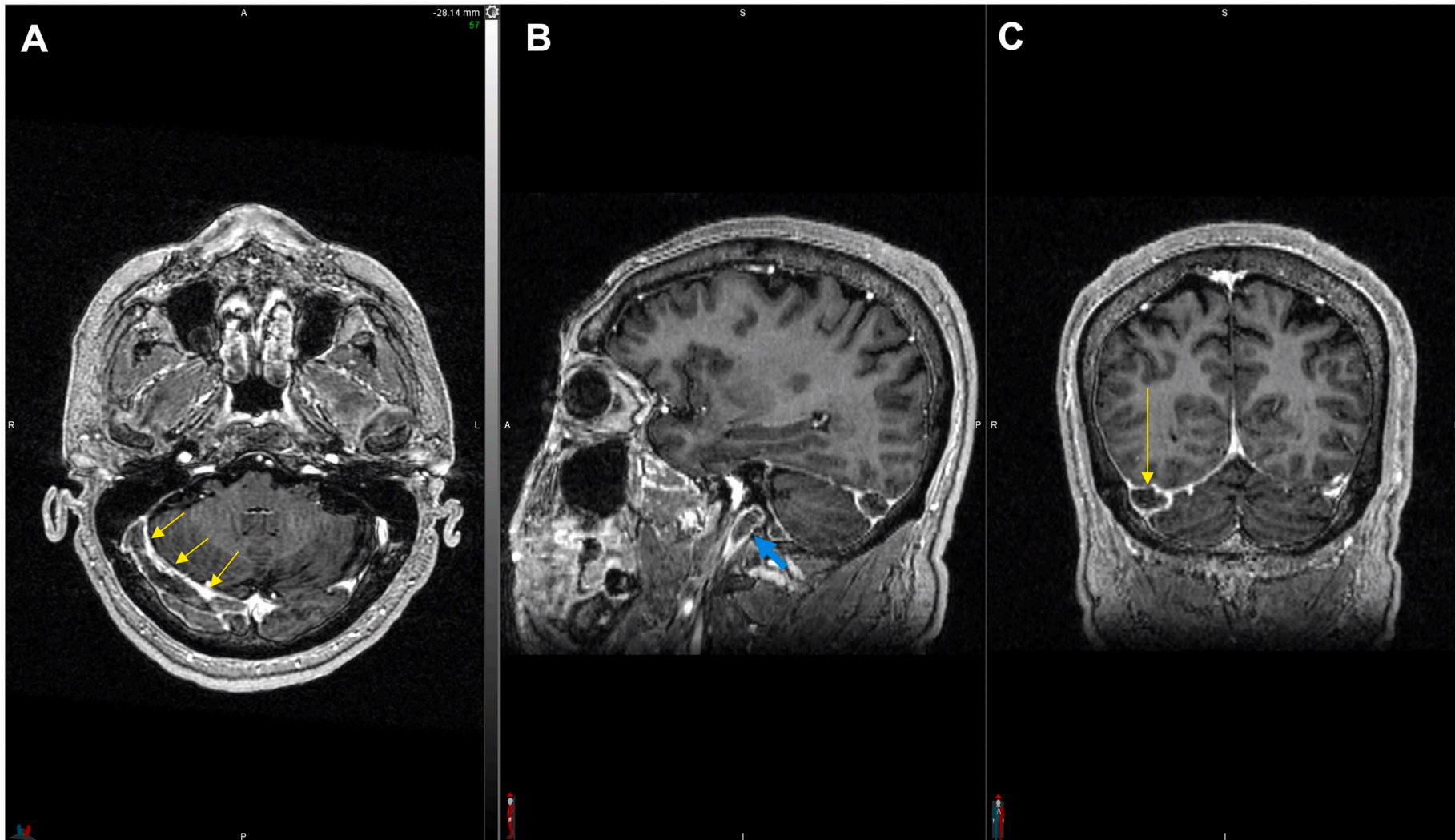


Fig. 4. MRI 3D T1 MPRAGE post gadolinium contrast A) axial, B) sagittal, C) coronal, central absent enhancement right transverse and sigmoid sinuses (yellow arrows), and proximal right internal jugular vein (blue arrow), with no intracranial hemorrhage or infarction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

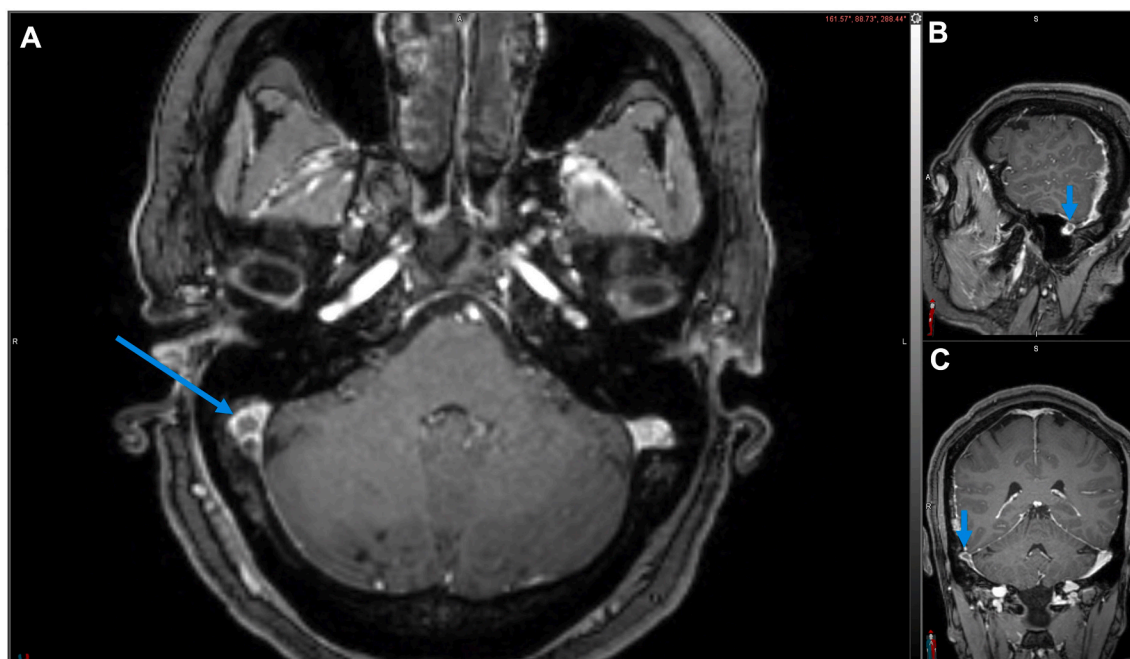


Fig. 5. MR venogram A) axial, B) sagittal and C) coronal contrast-enhanced demonstrates a filling defect within the right transverse-sigmoid sinus junction and extending into the proximal right sigmoid sinus (blue arrows), consistent with venous sinus thrombosis. (For interpretation of the references 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 venography volumes in March/April 2021 was 622% for CTV and 221% for MRV, compared to 2018–2020. [Fig. 1].

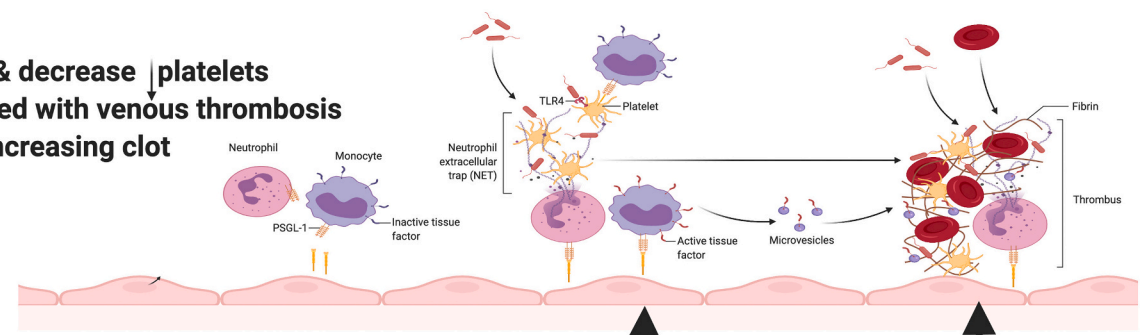
4. Discussion

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.

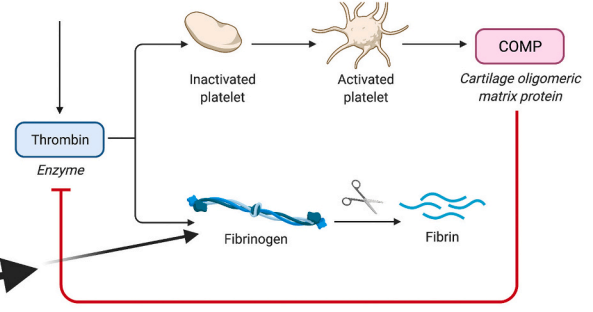
Cross-sectional CT or MR venography both have a high sensitivity and specificity for diagnosing CVT. Advantages of CT include its ease of availability, rapid scan times, and absence of pre-screening. Disadvantages of CT include ionizing radiation exposure. MRI, provides superior soft tissue visualization, and can be performed without contrast and ionizing radiation. Limitations for MRI include safety considerations

**Adenoviral capsid - PF4+ = novel antigen,
 Monocytes, B-cell form anti-PF4 (VITT) Abs attack & decrease platelets
 Fibrinogen & active tissue factor increase associated with venous thrombosis
 Neutrophil extracellular traps (NET) trap platelets increasing clot
 Leads to Central Venous Thrombosis (CVT)
 Vaccine Induced Thrombocytopenia (VITT)**

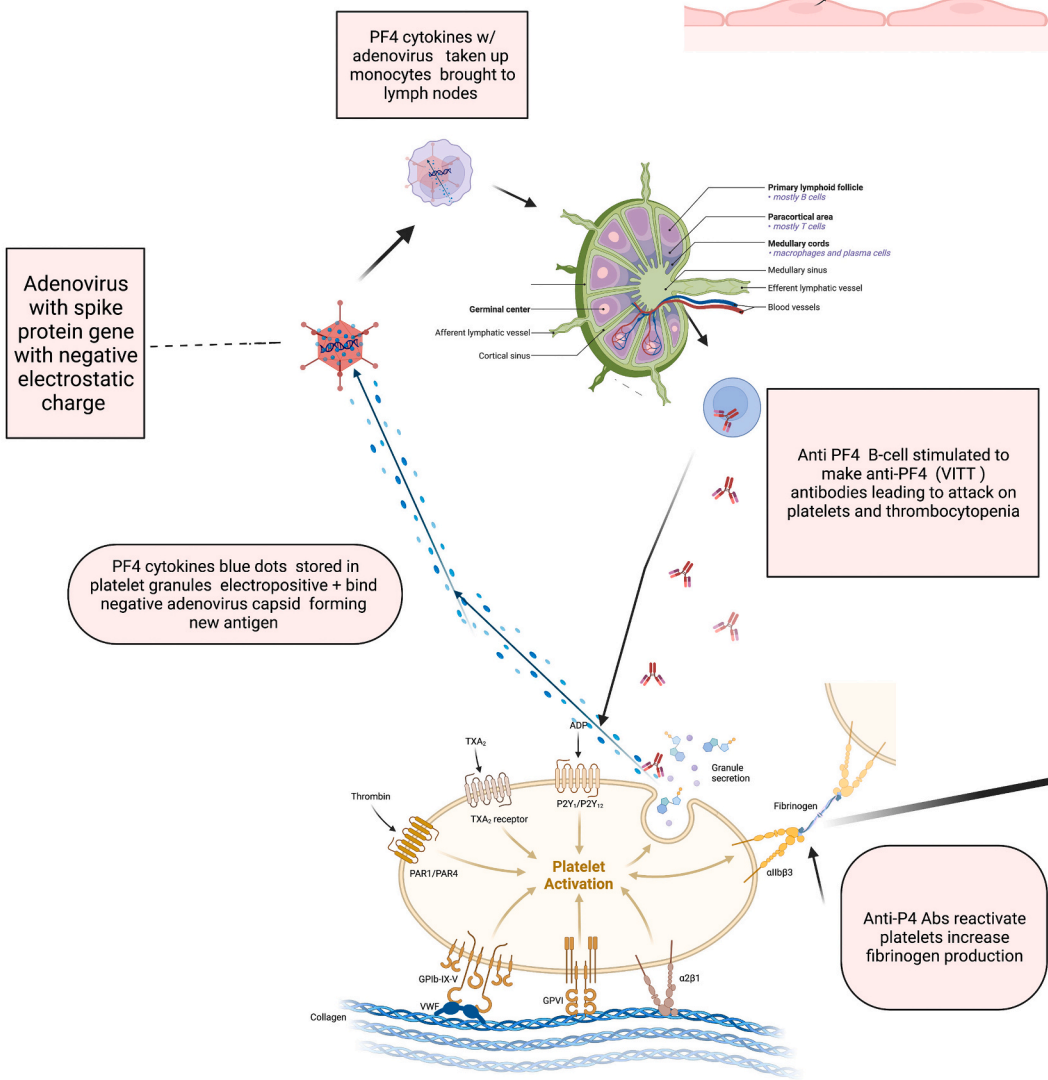


fibrinogen, D-dimer increase,
 Increased active tissue factor associated with
 Central venous thrombogenesis

Platelets continually attacked & reactivated
 by VITT Ab, decrease over time
 Increased fibrinogen broken down to fibrin
 Progressive clot formation



COMP inhibits:
 • Thrombin conversion of fibrinogen to fibrin
 • Thrombin-induced platelet activation



Anti PF4 B-cell stimulated to
 make anti-PF4 (VITT)
 antibodies leading to attack on
 platelets and thrombocytopenia

Anti-P4 Abs reactivate
 platelets increase
 fibrinogen production

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 of anti-PF4 memory B-cells and anti-PF4 (VITT) antibodies.^{14-17,28-30} 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.⁴¹ Platelet trapping leads to clot formation and progressive thrombocytopenia.

for metallic hardware that maybe affected by magnetic fields, such as a cardiac pacer, therefore requiring pre-screening. In addition in 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 adenovirus 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 adenoviral vector encoding the spike glycoprotein of SARS-CoV-2.

In Europe, CVT thrombotic events with thrombocytopenia were observed following AstraZeneca vaccine administration.^{23–25} 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.^{23–25} 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.²³ In Germany and Austria, Greinacher et al. described 11 patients with similar thrombosis and thrombocytopenia syndrome following AstraZeneca vaccination.²⁵ All patients had severe CVT, one patient presented with fatal intracranial hemorrhage, likely from CVT VITT.²⁵

Initial UK Medicine and Healthcare Products Regulatory Agency (MRHA) and European Medicines Agency (EMA), responses were “there is no evidence that blood clots in veins are occurring more than would be expected”.²⁶ 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 thrombotic thrombocytopenia (VITT).^{18,23,27,28}

In the United States, the Janssen/Johnson & Johnson, a human adenoviral vector, received Emergency Use Authorization (EUA) on February 27th 2021. By April 12th 2021, approximately 7 million Ad26.COV2-S vaccine doses were given in the USA, and 6 CVT VITT cases identified, primarily women younger than 40 years of age without prior thrombophilia.^{12,29,30} In early May 2022, after review of CVT VITT from COVID-19 adenoviral vector vaccines, the FDA limited the use of the Janssen COVID-19 vaccine.^{30, 31}

Cerebral venous thrombosis in COVID-19 may reflect maladaptive immune responses from cytokine storms, and viral tropism to ACE2 receptors that decreases ACE2 and Ang 1–7 causing hypercoagulability, hyperinflammatory endotheliopathy, and down regulation of vascular endothelial ACE2 expression, neutrophil extracellular traps and anti-phospholipid antibodies, as well formation of neutrophil extracellular traps.^{31–33}

In early 2021, during the vaccine roll out and reporting of CVT VITT, in this study, cross-sectional CT and MR venograms studies increased substantially, likely reflecting public and physician awareness with concern for CVT VITT. Of 202 venograms obtained in March and April 2021, 158 (78.2%) were on unvaccinated patients, with 16 positive for CVT (10.1%), and 44 were on vaccinated patients (21.7%), 8 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 %.^{21,25,34–40}

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.^{16,18,21} It is postulated the adenoviral 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.^{15,17–22} (Fig. 6).

The elevated levels of antibodies to platelet factor 4–polyanion complexes in CVT VITT, lead to computation analysis of the adenoviral ChAdOx1 viral vector capsid and receptor binding fiber knob protein interactions with CD46, coxsackie and adenovirus receptor (CAR), and the PF4 cytokine.³⁸ 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 adenoviral ChAdOx1 viral capsid surface electronegative charge, with PF4 binding the viral capsid, with a shape allowing it enter in between viral hexons.³⁸ (Fig. 6). 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.^{15,17–22} (Fig. 6)

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 adenoviral vector vaccines including the ChAdOx1 nCov-19 (Oxford-AstraZeneca) vaccine, a recombinant chimpanzee adenoviral 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 CVT 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, and 2 were positive for CVT (4.5%), (odds ratio = 0.52 [0.12–2.38], $p = 0.200$). CVT VITT has an incidence of 1/100,000 vaccinated individuals, a slight increased prevalence in women <60 years of age, although males may also be affected. The symptoms may present up to 5 to 20 days post-vaccination and present with a headache and the early neurologic exam can be non-focal. However, a high clinical suspicion should be maintained for the diagnosis, with cross-sectional CT or MRV venography, to assess for CVT, as progression of CVT in VITT has a 40% mortality.

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Declaration of competing interest

None.

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