Impact of COVID vaccination rollout on the use of computed tomography venography for the assessment of cerebral venous sinus thrombosis

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The authors declare that all authors had full access to all of the data in the study.

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Abstract

Introduction: Cerebral venous sinus thrombosis (CVST) is rare; however, it has been observed in patients with vaccine-induced immune thrombotic thrombocytopaenia syndrome (VITT) following the use of adenovirus vector vaccines against COVID-19. Adverse vaccine effects have been heavily addressed in mainstream media, likely contributing to vaccination anxiety. This study aimed to assess how the vaccine rollout and media coverage has influenced the use of computed tomography venography (CTV) in an acute care setting of a tertiary hospital.

Method: Single-centre retrospective cohort study from 30 March 2021 to 13 June 2021. Direct comparison to same calendar dates in the preceding 3 years.

Results: In 2021, 57 patients received CTV with headache being the reason in 48 (84%) and 40 (70%) had received ChAdOx1 nCov-19 (AstraZeneca COVID-19 vaccination). Only 20 of these patients received CTV after platelets and D-Dimer had returned, and only three patients met existing guidelines for imaging. Zero cases were positive. The number of CTV studies was 5.2 times than in 2020 and 2.7 times the mean number for the 3 preceding years.

Conclusion: The use of CTV in patients with headache has markedly increased at our centre since negatively biased vaccination influence of mainstream media. Headache is a common vaccine-related side effect and VITT is exceptionably rare. With the rates of vaccination increasing in the community, these results highlight the importance of strict adherence to established evidence-based guidelines. Otherwise, critical care capacity, and in particular imaging resources already under pressure will be strained further.

Key words: AstraZeneca; COVID; CVST; thrombus; vaccine.

Introduction

Cerebral venous sinus thrombosis (CVST) is rare, accounting for <1% of stroke admissions and a has a low population incidence of 0.22–1.57 per 100,000.1,2 A small number of CVST have been observed in patients following vaccination against severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV2 or COVID-19) with adenovirus vector vaccines;3,4 more specifically, following the use of either ChAdOx1 nCov-19 (AstraZeneca COVID-19) or Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19).3,4 The former is the only provisionally registered adenovirus vector vaccine for use in Australia at time of writing.5 A second vaccine is provisionally registered in Australia, BNT162b2 (Pfizer-BioNTech), and is based on mRNA technology and not known to cause thrombotic thrombocytopaenic syndrome.6,7

This novel thrombosis syndrome known as vaccine-induced immune thrombotic thrombocytopaenia syndrome (VITT) is caused by autoantibodies to platelet factor 4 (PF4).7 VITT is reported to be a rare condition occurring between day 5 and 30 post vaccination and results in thrombosis in both typical sites (e.g. pulmonary embolism) and unusual sites (e.g. splanchic circulation...
and cerebral veins) with diagnostic criteria detailed in Table 1. Exposure to ChAdOx1 nCov-19, (AstraZeneca) within 4-30 days of symptom onset.

Thrombocytopenia or falling platelet count and elevated D-Dimer (>5 times upper limit normal) or reduced fibrinogen.

Thrombosis: Any deep vein thrombosis, pulmonary embolism or arterial thrombosis. Thrombosis in uncommon sites, such as CVST and splanchnic vein thrombosis, is strongly suggestive.

Antibodies detected against PF4/polyanion. Functional assay indicating patient-derived plasma/serum induction of prothrombotic phenotype in healthy donor platelets.

Patient details and definitions

Data collection included demographics, presenting symptom and diagnosis (positive or negative for CVST). For patients who were examined in 2021 additional collected data included platelet levels, D-Dimer, vaccination details (type of vaccination and number of days from injection to presentation), if applicable.

Outcomes

The primary outcome was to assess the number of positive CTV scans in 2021 to identify the incidence rate and compare this to preceding years.

Statistical analysis

Data were collated using Microsoft Excel (Microsoft, USA) and expressed as number (percentage), mean (SD) or median (IQR) according to the data type. Data were assessed for significance using Student’s t-test and binary logistic regression according to the relative data type and outcome. A two-tailed P-value of <0.05 was considered statistically significant.

Results

A total of 57 patients were referred for CTV in an acute care setting between 31 March 2021 and 13 June 2021 (Figure 1) and there were zero patients diagnosed with CVST. The mean age was 54.3 years (SD 19.7), and the majority (80.7%) were females as shown in Table 2.

A total of 64 patients were identified in the same study period window for the three previous consecutive years combined, or 21.3 per year and there were two patients diagnosed with CVST. The incidence rate in 2018 was 1 per 27, 1 per 26 in 2019 and 0 per 11 in 2020. Significance testing comparing 2021 to the preceding years was not possible due to the zero incidence in 2021. The mean age for the 2018–2020 population was 41.5 years (SD: 15.2, P = 0.346). Headache was the primary presenting complaint for both the 2021 (84.2%) and 2018–2020 cohorts (76.6%, P = 0.295). Other presenting complaints included stroke symptoms, decreased consciousness, eye symptoms and facial or ear inflammatory processes.

Vaccination population details

As shown in Table 3, 40 of 57 patients were referred this year (2021) for CTV following EMR documentation of AstraZeneca vaccination at a median of 10 days following vaccination (IQR 7.25). No patients were referred for CTV in this study period following Pfizer vaccination. Thirty-two patients (80%) had both full blood count (including platelets) and a D-Dimer test in the emergency

| Table 1. Thrombosis and Haemostasis Society of Australia and New Zealand diagnostic criteria for VITT |
|---------------------------------------------|
| Exposure to ChAdOx1 nCov-19, (AstraZeneca) within 4-30 days of symptom onset. |
| Thrombocytopenia or falling platelet count and elevated D-Dimer (>5 times upper limit normal) or reduced fibrinogen. |
| Thrombosis: Any deep vein thrombosis, pulmonary embolism or arterial thrombosis. Thrombosis in uncommon sites, such as CVST and splanchnic vein thrombosis, is strongly suggestive. |
| Antibodies detected against PF4/polyanion. Functional assay indicating patient-derived plasma/serum induction of prothrombotic phenotype in healthy donor platelets. |

| Research ethics standards compliance |
|-------------------------------------|
| Ethical approval was provided by the institutional research and ethics committee, including a waiver of consent. |

| Population |
|------------|
| Retrospective cohort study in an acute care setting for CTV between 31 March 2021 and 13 June 2021. Patients were identified through the Radiology Information System and Electronic Medical Record (EMR). This 75-day period begins at the date from early reported concerns in Australian media regarding CVST post vaccination. Further data were collected from the same calendar dates for the three consecutive preceding years, to allow for comparison. Patients were excluded if the indication for CTV was blunt force trauma. All other patients above the age of 18 years were included in the study. |

| Outcomes |
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| Statistical analysis |
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department. Twelve patients (40%) underwent CTV prior to pathology collection or results available for review. Three (7.5%) AstraZeneca patients met Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) criteria for imaging.3

Discussion

Cohorts in this study were of similar gender and presenting symptom of which headache was the most common. In 2021, the mean age was significantly higher than for preceding years (54.3 vs. 41.5 years, \( P < 0.001 \)) which likely reflects the older demographic who were eligible for vaccination during the early phases of rollout.14

The number of CTV performed in 2021 was 2.7 times the mean number from the preceding 3 years and 5.2 times the number in 2020. The cause of this increase is multifactorial. The major factor behind scanning is likely related to patient anxiety in the context of abundant media coverage of vaccination complications. However, emergency department practitioners are also placed in a challenging situation, where National Emergency Access Targets encourage early scanning sometimes prior to availability of relevant differentiating tests, such as platelets and D-Dimer.15 In addition, it is likely that there is cognitive bias within emergency physicians whom are influenced by the community’s hyper vigilance on the background of an unprecedented and uncertain pandemic. As a result, over 90% of the patients in this study following AstraZeneca vaccination did not meet imaging criteria for VITT-associated CVST as in Table 1.3

Table 2. Comparison of CT brain venogram studies performed 31 March to 13 June in 4 consecutive years

|                  | 2021       | 2020       | 2019       | 2018       | 2018–2020 combined | \( P \)-value† |
|------------------|------------|------------|------------|------------|-------------------|---------------|
| Female gender (n, %) | 46 (80.7%) | 8 (72.7%)  | 21 (80.8%) | 18 (66.7%) | 47 (73.4%)         | OR 1.513, \( P = 0.346, 95\% \text{ CI: 0.640–3.576} \) |
| Age (mean, SD)    | 54.3 (19.7) | 37.7 (14.8) | 43.0 (16.4) | 41.5 (14.4) | 41.5 (15.2)        | \( P < 0.001, 95\% \text{ CI: 6.552–19.146} \) |
| Headache as presenting symptom (n, %) | 48 (84.2%) | 8 (72.7%)  | 20 (76.9%) | 21 (77.8%) | 49 (76.6%)         | OR 1.6, \( P = 0.295, 95\% \text{ CI: 0.652–4.086} \) |
| Number of scans (n) | 57         | 11         | 26         | 27         | 64                | N/A           |
| Number of positive (n, %) | 0          | 0          | 1 (3.8%)   | 1 (3.7%)   | 2 (3.1%)          | N/A†         |

†Comparing 2021 to 2018–2020
‡Unable to compare odds given the incidence of zero in 2021.

Table 3. Vaccine statistics for patients in 2021 presenting with headache and receiving CT venography

|                              | Number of Pfizer vaccinations | Number of AstraZeneca vaccinations | Day of presentation post AstraZeneca (median, IQR) | AstraZeneca patients who met criteria for VITT (n, %) |
|------------------------------|--------------------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|
|                              | 0                              | 40                                | 9.5 (7.25)                                    | 3 (7.5%)                                      |
Computed tomography venography is the first-line investigation for CVST in Australia as it is accurate, reproducible and rapidly available. It has also been proven to be as accurate as magnetic resonance venography (MRV) for the diagnosis of CVST without the costs and resources required to generate MRV.\textsuperscript{2,16} However, the use of CTV is not without risk, including ionizing radiation exposure, contrast allergic reaction and contrast nephropathy.\textsuperscript{2} Majoei et al.\textsuperscript{17} estimate the effective dose for a CT venogram to approximate 1.4 mSv. This is below a threshold for tissue effects; however, stochastic effects are cumulative, and any potentially unnecessary ionizing radiation may contribute to a later lifetime risk of cancer. The risk of death following contrast administration is approximately 0.9 per 100,000.\textsuperscript{18} In comparison, Australian authorities report the incidence of VTTS as 3.1 per 100,000 for <50 years and 1.8 per 100,000 for those 50 years, with death rate reported to be 25% for VTTS.\textsuperscript{19,20} In Australia, at time of writing, there have been two confirmed deaths out of 3.8 million doses (0.05/100,000 doses).\textsuperscript{21} A significant factor also to consider in a tertiary emergency department is opportunity cost when there are many other patients concurrently awaiting diagnostic scanning in a setting where resources are limited.

Worldwide understanding of VITT is rapidly increasing for this novel complication following SARS-CoV2 adenovirus vector-based vaccines. Clinical guidelines and treatment strategies for VITT were first published in Australia by THANZ on 1 April 2021 and include advice for the use of radiological investigations in the assessment of organ-specific thrombosis.\textsuperscript{3} Similar guidance has been released in June by the Australian College of Emergency Medicine.\textsuperscript{22}

There is now a guideline from the Royal Australian and New Zealand College of Radiologists (RANZCR) based upon the THANZ principles, with practical considerations for emergency physicians and radiologists to follow.\textsuperscript{23} RANZCR recommendations are for patients who have been given the AstraZeneca vaccine within the last 4–42 days, and present with persistent headache, visual changes, focal neurological symptoms, seizures or coma-tose. The use of diagnostic CTV is suggested in those where VITT is considered “possible” or “probable”.\textsuperscript{3} Practically, this is defined as D-Dimer > 5 times the upper limit of normal and platelets less than 150 × 10\textsuperscript{9}/L. Alternatively, where platelets are normal, CTV may also be considered if symptoms persist but should be based on clinical judgement.\textsuperscript{3,23}

Based on this guidance, only three (7.5%) of AstraZeneca-vaccinated patients presenting to our institution in this study period met guidelines for investigation of organ-specific thrombosis. One patient was subsequently ‘VITT confirmed’ following evidence of thrombosis (positive CT pulmonary angiogram) and identification of PF4 antibodies on ELISA testing;\textsuperscript{3} although this patient did not have CVST.

This retrospective study has limitations to acknowledge. It is reliant on the EMR and is thus prone to documentation error. The study period is short and underpowers assessment of trend analysis particularly in a rapidly changing environment. The understanding of VITT is rapidly evolving and decision-making guidelines take time to be developed, disseminated and educated prior to any change in medical care. Given that the THANZ guidelines were released at the beginning of the study period, they may not have been widely known at time of care delivery.

In conclusion, this study showed that the use of CTV in patients with headache has markedly increased at our centre since identification of VITT and the subsequent negatively biased vaccination influence of mainstream media. Headache is a common vaccine-related side effect and VITT is an exceptionally rare, serious and potentially fatal condition. With the rates of vaccination increasing in the community, these results highlight the importance of strict adherence to established evidence-based guidelines. Otherwise, critical care capacity, and in particular imaging resources already under pressure will be strained further.

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Data availability statement
Author elects to not share data.

References
1. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis. Stroke 2012; 43: 3375–7.
2. Saposnik G, Barinagarrementeria F, Brown RD \textit{et al.} Diagnosis and management of cerebral venous thrombosis. Stroke 2011; 42: 1158–92.
3. Chen V, Curnow JL, Tran H, Choi PYI. Australian New Zealand approach to diagnosis and management of vaccine induced immune thrombosis and thrombocytopenia. Med J Aust 2021; 215: 245–9.
4. Cines DB, Bussel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. N Engl J Med 2021; 384: 2254–6.
5. The Therapeutic Goods Administration. COVID-19 vaccine: AstraZeneca ChAdOx1-S. 2021 Mar 26 [cited 21 Jun 2021]. Available from URL: https://www.tga.gov.au/covid-19-vaccine-astrazeneca-chadox1-s
6. The Therapeutic Goods Administration. TGA provisionally approves Pfizer COVID-19 vaccine. 2021 Jan 25 [cited 21 Jun 2021.] Available from URL: https://www.tga.gov.au/media-release/tga-provisionally-approves-pfizer-covid-19-vaccine
7. Scully M, Singh D, Lown R \textit{et al.} Pathologic antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021; 384: 2202–11.
8. The Therapeutic Goods Administration. COVID-19 vaccine weekly safety report. 17-06-2021. 2021 Jun 17 [cited 21 Jun 2021.] Available from URL: https://www.tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-17-06-2021
9. Jemielniak D, Krempovych Y. # AstraZeneca vaccine disinformation on Twitter. medRxiv. 2021: Prepint posted online April 8, 2021. https://doi.org/10.1101/2021.04.08.21255107
10. Edwards B, Biddle N, Gray M, Sollis K. COVID-19 vaccine hesitancy and resistance: correlates in a nationally representative longitudinal survey of the Australian population. PLoS One 2021; 16: e0248892.
11. Comerford D, Olivarius O, Bell D et al. Did negative news regarding the Oxford AstraZeneca vaccine end in vaccine hesitancy? A repeated cross-section event study from the UK. Research Square 2021. https://doi.org/10.21203/rs.3.rs-355311/v2
12. Mattiuzzi C, Lippi G. Headache after COVID-19 vaccination: updated report from the Italian Medicines Agency database. Neurol Sci 2021; 42: 3531–2.
13. Alfred Health. The Alfred Health annual report 2019-2020. 2020 Dec 19 [cited 23 Jun 2021.] Available from URL: https://www.alfredhealth.org.au/images/resources/corporate-publications/Annual-Report/Alfred-Health-Annual-Report-2019-2020.pdf
14. MacIntyre CR, Costantino V, Trent M. Modelling of COVID-19 vaccination strategies and herd immunity, in scenarios of limited and full vaccine supply in NSW, Australia. Vaccine 2021. https://doi.org/10.1016/j.vaccine.2021.04.042
15. Clements W, McMahon GAL, Joseph T et al. Risk stratification of emergency department patients with acute pulmonary thromboembolism: Is chest pain a reason to investigate? J Med Imaging Radiat Oncol 2021. https://doi.org/10.1111/1754-9485.13262
16. Khandelwal N, Agarwal A, Kochhar R et al. Comparison of CT venography with MR venography in cerebral sinovenous thrombosis. AJR Am J Roentgenol 2006; 187: 1637–43.
17. Majoe CBLM, van Straten M, Venema HW, den Heeten GJ. Multisection CT venography of the dural sinuses and cerebral veins by using matched mask bone elimination. Am J Neuroradiol 2004; 25: 787–91.
18. Caro JJ, Trindade E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. Am J Roentgenol 1991; 156: 825–32.
19. Australian Technical Advisory Group on Immunisation. ATAGI update following weekly COVID-19 meeting - 2 June 2021. 2021 Jun 4 [cited 21 Jun 2021.] Available from URL: https://www.health.gov.au/news/atagi-update-following-weekly-covid-19-meeting-2-june-2021
20. Australian Technical Advisory Group on Immunisation. ATAGI statement on AstraZeneca vaccine in response to new vaccine safety concerns. 2021 Apr 8 [cited 21 Jun 2021.] Available from URL: https://www.health.gov.au/news/atagi-statement-on-astrazeneca-vaccine-in-response-to-new-vaccine-safety-concerns
21. ABC. Second woman dies from extremely rare blood clots likely linked to AstraZeneca COVID-19 vaccine. 2021 Jun 10 [cited 21 Jun 2021.] Available from URL: https://www.abc.net.au/news/2021-06-10/woman-dies-rare-blood-clots-astrazeneca-covid-vaccine/100205652
22. Australasian College of Emergency Medicine. Thrombosis with thrombocytopenia syndrome following COVID-19 vaccination. Assessment of patients presenting to the Emergency Department with TTS symptoms. v2.0. https://acem.org.au/Content-Sources/Advancing-Emergency-Medicine-COVID-19/Resources [updated 2021 Jun; cited 2021 Jun 21].
23. Royal Australian and New Zealand College of Radiologists. Imaging Recommendations for Patients Suspected of VITT [internet]. Accessed 9/20/2021. Available from URL: https://www.ranzcr.com/documents-download/other/5316-20210604-ranzcr-vitt-imaging-guideline