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Incidence of thrombocytopenia-associated cerebral venous sinus thrombosis: a population-based study

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ABSTRACT

Objectives The identification of SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia (VITT) followed the recognition of a hitherto uncommon clinical syndrome frequently associated with cerebral venous sinus thrombosis (CVST), termed 'thrombosis with thrombocytopenia' syndrome (TTS). While anecdotally recognised as rare, the background incidence of TTS is unknown. We therefore aimed to investigate the background incidence of CVST with TTS in a large, well-defined population-based CVST cohort.

Methods We performed an analysis of our previously obtained retrospective population-based cohort of patients with CVST from Adelaide, Australia (2005–2011, comprising an adult population of 953 390) to identify the background incidence of CVST associated with TTS.

Results Among 105 people with CVST, the background population-based incidence of TTS-associated CVST was 1.2 per million per year (95% CI 0.5 to 2.4). A single case of a severe CVST VITT-like syndrome with multiorgan thrombosis was identified, occurring 3 weeks postrotavirus infection.

Conclusions In our population-based study, the background incidence of CVST with associated TTS was very low, and the sole clinically severe case with multiorgan thrombosis occurred following a rotaviral precipitant. Our study establishes a benchmark against which to measure future potential 'TTS' clusters and suggests that viruses other than adenovirus may trigger this syndrome.

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) occurs in approximately half of vaccine-induced immune thrombotic thrombocytopenia (VITT) cases.[1] VITT is a syndrome resembling heparin-induced thrombocytopenia and is associated with ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson) adenoviral vector vaccines against SARS-CoV-2. VITT most often occurs within 2 weeks postvaccination and is associated with platelet-activating antiplatelet factor 4 (PF4) antibodies.[2] The incidence of VITT-associated CVST is approximately 1:100 000 among patients aged less than 50 years and 1:200 000 in those aged ≥50 years.[1] Where definitive testing for antiPF4 antibodies has been unavailable, a homologous diagnosis of 'thrombosis with thrombocytopenia syndrome' (TTS) may be made.[2]

While circumstantial and experimental evidence linking these vaccines with VITT is compelling, to complete standard epidemiological causal criteria, unbiased assessments of association strength and specificity are required. In order for this to occur, both the background population incidence of CVST as well as the natural incidence of CVST meeting operational TTS criteria need to be clarified.[2]

Although a single previous pooled cohort study provided evidence that thrombocytopenia-associated CVST is uncommon in those unexposed to the vaccine,[2] this non-population-based cohort was drawn from likely unrepresentative institution-based samples. Additionally, missing platelet counts were common.

We previously performed a population-based study of CVST over 7 years in Adelaide, Australia, using a novel method to maximise ascertainment, reporting a CVST incidence of 15.7 per million per year (95% CI 12.9 to 19).[3] Therefore, we used this cohort to investigate the background incidence of TTS-associated CVST.

METHODS

The broad method of our study has been previously described.[3] For the purpose of the current analysis, we examined all 105 cases of CVST from this cohort to determine the proportion that met Level 1 Brighton criteria for TTS[4] (ie, thrombosis with a new onset of a platelet count of $<150\times10^9$/L). 'New onset' was defined as thrombocytopenia with an obtainable presymptomatic normal result or thrombocytopenia without a documented

medical history of this. We excluded cases with only one thrombocytopenic recording (n=3) to exclude those with possible clumping artefacts. We subsequently assessed cases for the presence of a 'VITT-like' illness by reviewing the clinical data and investigations. Incidence rates were calculated per million per year, with CIs calculated from the Poisson distribution. The waiver of consent was provided by the ethics committees of all Adelaide public hospitals.

RESULTS

Only eight of 105 cases (8%) presented with CVST associated with new-onset thrombocytopenia, yielding a population-based incidence of TTS-associated CVST of 1.2 per million per year (95% CI 0.5 to 2.4). This is approximately 90 times less frequent than figures observed in the first 2 weeks following vaccination in the UK.[1] CVST-associated intracerebral and subarachnoid haemorrhage seemed more frequent among those with TTS than in those without (table 1), acknowledging small sample sizes. None had tested for PF4 antibodies, as these were not commercially available at the time, and blood samples were not prospectively stored.

Clear explanations for thrombocytopenia were present in four out of eight patients with TTS-CVST (malignancy (n=2), antiphospholipid syndrome (n=1) and severe trauma (n=1)). Three of the remaining cases only had mild thrombocytopenia, with platelet nadir counts ranging from 119×10^9/L to 134×10^9/L. Heparin exposure could not be reliably determined; however, no case had a clear indication pre-CVST for therapeutic heparinisation.

Only one case of 105 resembled the full VITT phenotype of extensive multiorgan thrombosis and severe otherwise unexplained thrombocytopenia, giving a 'VITT-like' TTS-CVST case occurrence of one in 80.04 million person-months. A woman in her 20s with an unremarkable history presented after 3 days of headache, rash, nausea and vomiting, 3 weeks following a rotavirus infection. Imaging demonstrated right parieto-occipital intracerebral haemorrhage, venous infarction and sagittal sinus thrombosis. Initial platelet count was 45×10^9/L, 40 at nadir. D-dimer was raised (3.54 mg/L), and fibrinogen was mildly low. Following platelet transfusion, an emergency craniotomy for transtentorial herniation was performed; histology demonstrated haemorrhagic venous infarction with cortical venous (and one small arterial) thrombus. The heparin infusion was subsequently initiated. Venous thrombectomy recanalised the sagittal sinus but not the extensive bilateral cortical vein thrombosis. Iliac artery thrombosis was also demonstrated. Thrombophilic screening was negative, including genetic thrombophilias, paroxysmal nocturnal haemoglobinuria and antiphospholipid syndrome. Despite bifrontal decompression (day 3), the patient did not recover consciousness and died on day 11.

Table 1 Clinical characteristics of patients with CVST, according to TTS status

	TTS n=8 n (%)	No TTS n=97 n (%)
Demographics		
Age in years, mean (range)	54 (26–75)	50 (19–84)
Female sex	4 (50)	51 (53)
CVST risk factors		
Hormonal	1 (13)	16 (16)
Other drug	0 (0)	1 (1)
Thrombophilia	1 (13)	13 (13)
Other haematological	2 (25)	9 (9)
Cancer	2 (25)	24 (25)
Parameningeal infection	0 (0)	6 (6)
Intracranial infection	0 (0)	4 (4)
Mechanical precipitant	2 (25)	10 (10)
Other	0 (0)	32 (33)
Clinical presentation of CVST		
Headache	3 (38)	47 (48)
Focal neurological deficits	3 (38)	31 (32)
Seizure	1 (13)	18 (19)
Coma	3 (28)	7 (7)
Nausea/vomiting	2 (25)	12 (12)
Neck pain	0 (0)	7 (7)
Photophobia	0 (0)	7 (7)
Dizziness	0 (0)	5 (5)
Diplopia	0 (0)	4 (4)
Asymptomatic	0 (0)	13 (13)
Other	3 (38)	15 (15)
Radiological findings		
Thrombosis location		
Superior sagittal sinus	2 (25)	15 (15)
Transverse sinus	1 (13)	11 (11)
Cavernous sinus	0 (0)	1 (1)
Sigmoid sinus	0 (0)	9 (9)
Straight sinus	0 (0)	1 (1)
Cortical vein	0 (0)	5 (5)
Multiple	5 (63)	55 (57)
Intracerebral haemorrhage	2 (25)	10 (10)
Subarachnoid haemorrhage	3 (38)	2 (2)
Ischaemia and infarction	1 (13)	19 (20)
Oedema	1 (13)	4 (4)
Clinical outcome		
Asymptomatic	3 (38)	56 (58)
Disabled	0 (0)	29 (30)
Dependent	1 (13)	3 (3)

Continued

Table 1 Continued

	TTS n=8 n (%)	No TTS n=97 n (%)
Died	4 (50)	9 (9)

CVST, cerebral venous sinus thrombosis; TTS, thrombosis with thrombocytopenia syndrome.

DISCUSSION

We demonstrate that the population-based incidence of thrombocytopenia-associated CVST is very low, and spontaneous CVST with a severe VITT-like illness is even rarer. In our series, the sole case with severe thrombocytopenia and multiorgan venous and arterial thrombosis occurred 3 weeks following a rotavirus illness. Although a single case and lacking anti-PF4 antibody confirmation, it is notable that this occurred within the time frame typical of VITT (5–30 days postvaccination) and with a similar platelet nadir (45×10^9/L vs a median of 47×10^9/L). In conjunction with a recently described case of a postadenovirus infection VITT-like illness in which PF4 antibodies were found,[5] our case strengthens the association between virus exposure (whether therapeutic or naturally occurring) and this syndrome. Although this is a single case, our report raises the possibility that viruses other than adenovirus may potentially cause this syndrome.

Study limitations include the retrospective design, the small TTS numbers and the absence of anti-PF4 testing. Our findings are, however, concordant with an 865-patient retrospective, multicentre (but not population-based) CVST study, which reported thrombocytopenia in 8.4% of CVST cases, severe thrombocytopenia in 0.5% and anti-PF4 antibodies in none of the 93 patients retrospectively testable.[2] For more definitive confirmation, a prospective multiregional population-based design including routine collection of blood for anti-PF4 testing is recommended.

Although the pathophysiology of VITT is well established, to fully meet the causal Bradford Hill epidemiological criteria, the 'strength' and 'specificity' of the association must be determined. This cannot occur without measuring the background population incidence of both CVST and CVST meeting TTS criteria.[2] Our study helps complete the causal epidemiological criteria for SARS-CoV-2 vaccination-associated TTS with CVST and provides a provisional benchmark of population incidence for comparison should this syndrome re-emerge in other future clinical settings.

Contributors JM and TK conceptualised the study. JM, TK, PS and AT contributed to the methodology. JM performed the initial data and statistical analysis with supervision from TK, PS and AT. JM wrote the original draft, which was edited and supported by PS, AT and TK. All the authors read and approved the final manuscript.

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