



Comment

Most cases of Thrombosis and Thrombocytopenia Syndrome (TTS) post ChAdOx-1 nCov-19 are Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)

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Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) is a recently recognised syndrome observed in a small number of individuals who received the ChAdOx1 CoV-19 vaccine and was first identified in March 2021. The main features are thrombocytopenia and thrombosis within 5–30 days of adenoviral SARS-CoV-2 vaccination, with markedly elevated levels of D-dimer and presence of anti-PF4 antibodies [1]. In a paper published in the current issue of the journal [2], authors from one of the groups that initially described the syndrome [3] report updated clinical and laboratory data on the German national cohort of VITT patients [2].

The report links data from two sources to provide a comprehensive overview of a subgroup of the patients. The clinical details were obtained from the 106 cases of thrombosis and thrombocytopenia syndrome (TTS) reported to the Paul-Ehrlich-Institute (PEI), the German Agency where adverse events are reported, following vaccination with the ChAdOx-1 nCoV-19 vaccine. 52(49%) of the 106 TTS patients had their anti-PF4 testing at the Greifswald laboratory, an internationally centre of excellence for anti-PF4 research and testing. All 52 TTS patients tested for anti-PF4 using an IgG ELISA were positive, considered as confirmation of the diagnosis as VITT. The characteristics of the German TTS and VITT cohorts are similar to those reported with VITT from the UK [1] (Table 1). The relative higher proportion of female patients in Germany compared to the UK, reflects the fact that more females received the ChAdOx-1 nCoV-19 vaccine in Germany [2].

TTS was proposed by the Brighton Collaboration to allow comparative data to be collected by regulatory authorities post vaccination [4]. It differs from VITT in that it does not relate to causation and relationship to anti-PF4 antibodies. It should be acknowledged that the

term TTS can include patients who experience coincidental thrombosis and thrombocytopenia unrelated to vaccination such as patients with cancer, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation and antiphospholipid antibody syndrome. In this paper, all 52 (49%) TTS patients who were tested for anti-PF4 antibodies were found to be positive. It is possible that these were the more typical VITT cases since those tested were more likely to have presented with cerebral venous sinus thrombosis (CVST).

It has been shown that when testing for anti-PF4 in patients with VITT, the rapid assays such as those employing chemiluminescence, fail to detect the antibodies, whilst the ELISA assays perform more reliably [5]. An important issue that arises is whether anti-PF4 functional testing to demonstrate platelet activating antibodies is required, since these assays are not widely available. Thiele and colleagues have shown that 50 of the 52 anti-PF4 ELISA positive patients were also positive in the functional assay, with the only two negatives being individuals who received high dose intravenous immunoglobulin (IVIg) before functional testing [2]. This observation suggests that functional testing is not required in the typical VITT cases and could be reserved for more complex situations.

Another important observation reported is that the Greifswald laboratory also tested samples from eight patients with

Table 1

Comparison of German TTS and VITT cases with the UK VITT cases. NR – Not reported, CVST – Central venous sinus thrombosis, ICH – intracranial haemorrhage, PE – Pulmonary embolism.

	TTS N (% or range) Germany Thiele et al. (in press)	VITT N (% or range) Germany Thiele et al. (in press)	VITT N (% or range) UK Pavord et al. (2021)
Number	106	52	220
Female	73 (69)	37 (71)	119 (55)
Age overall	NR	45.3 (19–76)	48 (17–79)
Male	49.6 (21–77)		
Female	51.3 (18–78)		
CVST	56 (53)	37 (71)	110 (50)
ICH in CVST	27 (48.2)	NR	40 (36)
PE	24 (23)	NR	63 (28.6)
Splanchnic	11 (10)	NR	41 (19)
Multiple	22 (21)	19 (37)	64 (29.1)
Fatal	21 (20)	12 (23)	49 (22)

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thrombocytopenia but no thrombosis, for anti-PF4 following ChAdOx-1 nCoV-19 vaccination and four of these were strongly positive. The importance of this is two-fold, firstly that the TTS diagnostic category fails to include this group of VITT patients and secondly clinicians should be aware that VITT can initially present without thrombosis in what has been termed the pre-VITT phase [6]. Pre-VITT is the full syndrome but without documented thrombosis on imaging; patients present with severe headache, thrombocytopenia, high D-dimer and anti-PF4 in the appropriate period post vaccination. A recent publication from Germany showed that failure to initiate treatment with anticoagulation and IVIG in patients with pre-VITT as soon as the diagnosis is made, can result in the subsequent development of CVST with potentially catastrophic consequences [6]. This is analogous to heparin-induced thrombocytopenia, a condition also mediated by anti-PF4 antibodies, where alternative anticoagulation must be instituted immediately to prevent the development of thrombosis [7].

A limitation of the Thiele study [2] is that the anti-PF4 results were only known for the 49% (52/106) of the TTS patients who were tested at the Greifswald laboratory. A second limitation is that the population studied was largely younger Caucasian and predominantly female because this was the initial group offered the ChAdOx-1 nCoV-19 vaccination in Germany. It is not clear how these results apply to other racial groups.

Understanding the true incidence and mortality of VITT is dependant on robust and consistent diagnostic criteria such as those used in the UK [1]. The studies by Thiele [2] and Pavord [1] showed that not all cases included in the TTS diagnostic category are confirmed as VITT and not all cases of VITT are included as TTS.

Contributors

Both authors contributed equally to the writing and revision of this manuscript

Declaration of Competing Interest

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References

- [1] Pavord S, Scully M, Hunt BJ, et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. *N Engl J Med* 2021 in press.
- [2] Thiele T, Weisser K, Schonborn L, et al. Laboratory confirmed vaccine-induced immune thrombotic thrombocytopenia: analysis of reported cases after vaccination with ChAdOx-1 nCoV-19 in Germany. *Lancet Regional Health - Europe* 2021. doi: 10.1016/j.lanepe.2021.100270.
- [3] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med* 2021;384(22):2092–101.
- [4] Brighton Collaboration; 2021. <https://brightoncollaboration.us/wp-content/uploads/2021/05/TTS-Interim-Case-Definitionv10.16.3-May-23-2021.pdf>. Accessed August 2, 2021.
- [5] Platton S, Bartlett A, MacCallum P, et al. Evaluation of laboratory assays for anti-platelet factor 4 antibodies after ChAdOx1 nCoV-19 vaccination. *J Thromb Haemost* 2021;19(8):2007–13.
- [6] Salih F, Schonborn L, Kohler S, et al. Vaccine-induced thrombocytopenia with severe headache. *NEJM* 2021 in press.
- [7] Greinacher A. Heparin-induced thrombocytopenia. *NEJM* 2015;373:252–61.