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EDITORIAL

The International Cerebral Venous Thrombosis Consortium report on cerebral venous thrombosis following vaccination against SARS-CoV-2

In this issue, Krzywicka and colleagues describe the cases of cerebral venous sinus thrombosis (CVST) following vaccination against SARS-CoV-2 reported to the European Medicines Agency (EMA) via their post-marketing pharmacovigilance system. They compare features and outcomes both between different vaccines, and with a historical dataset from three European hospitals on sporadic CVST pre-COVID-19 [1].

All the vaccines approved for use in European countries have exhibited a high degree of efficacy for preventing serious illness and death in what is otherwise often a lethal and disabling disease, and that context should not be forgotten. It is remarkable that we are in a position to compare rare complications of vaccination based on tens of millions of recipients only 18 months on from the first cases of the disease.

The study represents the largest case series of CVST following vaccination against COVID-19 yet reported, including 213 cases of post-vaccine CVST, 114 of whom had thrombocytopenia. The report adds to previous data that indicate the association of adenovirus vector-based vaccines, in this case the Oxford AstraZeneca vaccine ChAdOx1, with an unusual profile of CVST, different from that encountered in the pre-COVID-19 era or in association with mRNA-based vaccines [2-4]. In particular, there was a high incidence of thrombocytopenia, lower prevalence of traditional risk factors for venous thrombosis, and higher mortality. It seems likely that most of the patients with thrombocytopenia had vaccine-induced thrombotic thrombocytopenia (VITT) [2], although confirmation of this diagnosis by detection of platelet factor 4 antibodies was available in only 15 cases.

Post-marketing surveillance has many limitations, including a risk of reporting bias. Additional risk of bias is introduced in the context of the COVID-19 pandemic, for reasons including the understandably high media profile of vaccines, expedited timelines and extraordinary public scrutiny of efficacy and safety data (often by commentators unfamiliar with such data), politicization of vaccine approval and delivery, and variation in national vaccination strategies. As the authors point out, it is possible that notification of cases would be more likely in recipients of ChAdOx1, the vaccine that has received most negative media attention, than for other vaccines.

The median age of the patients with CVST after an mRNA vaccine was 56 years, more than a decade higher than was seen in the currently reported historical data (45 years) or expected from published historical data (37 years in [5]). While this observation might tempt speculation that CVST preferentially affects older recipients of mRNA vaccines, in reality it probably reflects no more than the prioritization of older adults for vaccination across European countries. The biasing of age distributions by vaccination policy provides the clearest illustration of the perils of comparing post-vaccine CVST and historical CVST cases. Even comparisons between different vaccines are challenging, as the choice of vaccine has not been random. There were differences in vaccine approval, availability and prioritization schemes in different territories. Initially older individuals were preferentially given mRNA vaccines in several European countries, while there were limited data on the safety of the ChAdOx1 vaccine in the elderly.

The authors note that critical information is missing from their study. They were unable to confirm the accuracy of CVST diagnosis. Furthermore, the denominator for the population administered each of the vaccines investigated is absent. Detail of clinical cases is very limited and may be selectively reported. While there were no reported instances of COVID-19 infection among reported post-vaccine CVST cases, polymerase chain reaction (PCR) test results were available in only 21%, so an association of some cases of CVST with COVID-19 infection rather than vaccination cannot be excluded, although this seems unlikely since thrombocytopenia is not reported in COVID-19-associated CVST [6].

The report confirms the very high mortality rate of 38% for CVST following ChAdOx1 vaccination. The relevance of this observation for decisions regarding vaccination cannot be considered, however, without taking account of the extreme rarity of this event. The risk of CVST following a first dose of the ChAdOx1 nCov-19 vaccine is estimated to be between 5 and 10 cases per million doses (Schulz et al., 2021; [7,8]). Catching COVID-19 is far more hazardous. Even if we only consider the risk of brain injury, it has been estimated that around one-third of patients with COVID-19 develop a neurological or psychiatric diagnosis within 6 months of the infection [9].

This report will be welcome to clinicians seeking data to guide their management of the entirely new condition of VITT-associated CVST, as until recently they had to rely on anecdotal evidence from

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colleagues, case reports and very small series. The large dataset presented here represents a significant progress in our understanding of this condition, alongside the smaller but more detailed case series from the UK [4].

CONFLICT OF INTEREST

Keith W. Muir reports no conflicts of interest.

Richard J Perry was the lead author for the CAIAC Study (Cerebral venous thrombosis After Immunisation Against COVID-19) cited here as reference 4. He receives funding from The Stroke Association for the SETICOS study (Study Examining The Impact of COVID-19 On Stroke) and from Randox Laboratories for VOBIS (Validation Of Bioarray In Stroke), both unrelated to vaccination against COVID-19.

AUTHOR CONTRIBUTIONS

Keith W. Muir: Writing-original draft (equal); Writing-review & editing (equal). **Richard J Perry:** Writing-original draft (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

Not applicable.

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REFERENCES

1. Krzywicka K, Heldner M, Sanchez Van Kammen M, et al. Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European Medicines Agency. *Eur J Neurol*. 2021;28:3656-3662. 10.1111/ene.15029
2. Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. 2021;384:2202-2211.
3. Thakur KT, Tamborska A, Wood GK, et al. Clinical review of cerebral venous thrombosis in the context of COVID-19 vaccinations: evaluation, management, and scientific questions. *J Neurol Sci*. 2021;427:11753.
4. Perry RJ, Tamborska A, Singh B, et al. Cerebral venous sinus thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. *Lancet* online first. 2021. 10.1016/S0140-6736(21)01608-1
5. Ferro JM, Canhão P, Stam J, et al. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35:664-670.
6. Taquet M, Husain M, Geddes JR, et al. Cerebral venous thrombosis and portal vein thrombosis: a retrospective cohort study of 537,913 COVID-19 cases. *EClinicalMedicine*. 2021;31:101061. 10.1016/j.eclinm.2021.101061
7. Schulz JB, Berlit P, Diener H-C, et al. COVID-19 vaccine-Associated cerebral venous thrombosis in germany. *Ann Neurol*. 2021;1-13. https://doi.org/10.1002/ana.26172
8. Medicines & Healthcare Products Regulatory Agency Coronavirus vaccine – weekly summary of Yellow Card reporting. 2021. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reportingaccessed on 02/08/2021.
9. Taquet M, Geddes JR, Husain M, et al. 6-Month neurological and psychiatric outcomes in 236379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021b;8:416-427.