Is the heparin-induced thrombocytopenia-like syndrome associated with ChAdOx vaccine related to the vaccine itself or to an autoimmune reaction to severe acute respiratory syndrome 2 coronavirus: insights and implications from previous reports in infected cases?

A. AbdelMassih1,2, R. Hozaien3, M. El Shershaby3, A. Kamel3, H-A Ismail3 and R. Fouda4
1) Paediatric Cardiology Unit, Paediatrics Department, Faculty of Medicine, Cairo University, 2) Paediatric Cardio-Oncology Department, Children Cancer Hospital of Egypt, 3) Research Accessibility Team, Student and Internship Research Programme and 4) Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Abstract

Prothrombotic states, similar to heparin-induced thrombocytopenia (HIT) in recipients of the ChAdOx vaccine, sounded alarm bells internationally. Equivalent episodes of HIT were detailed in several case reports of coronavirus disease 2019. This suggests a common pathogenesis and warrants a shift in the management of implicated cases.

© 2021 The Author(s). Published by Elsevier Ltd.

Keywords: Adenovirus mediated vaccines, avoidance of heparin related anticoagulants, ChAdOx vaccine, COVID-19, PF4 antibodies, thrombotic thrombocytopenic purpura

Original Submission: 4 April 2021; Revised Submission: 7 April 2021; Accepted: 19 April 2021
Article published online: 23 April 2021

Background

Over 150 coronavirus vaccines are currently under development. In an attempt to stop the ongoing pandemic, numerous countries have issued emergency use authorization for a number of those vaccines [1]. This hectic vaccine rollout means that not enough is known about their short-term and long-term consequences. In March 2021, reports appeared of strokes and prothrombotic states in recipients of the ChAdOx vaccine (AZD1222, AstraZeneca, Cambridge, UK). The vaccine was temporarily suspended in several European countries [2].

The European Medicines Agency stated concern for the safety of the ChAdOx vaccine. However, Greinacher et al. revealed (in a preprint) the serological profile of patients who developed this unusual set of symptoms after the ChAdOx vaccine [3]. They concluded that the prothrombotic state in these patients is similar to heparin-induced thrombocytopenia (HIT). All nine patients showed positive anti-platelet factor 4 antibodies (anti-PF4), frequently seen in recipients of heparin. None of these patients were on heparin before vaccination. This implies that the ChAdOx vaccine can potentially induce such autoantibodies [3]. EMA temporarily suspended the use of ChadOx vaccine then confirmed that its benefits outweighs the prevalence of the observed complication.
Is this an old, misinterpreted feature of Coronaviridae or is it a brand new feature?

Some cases of HIT were reported before the current vaccine rollout; these are reviewed and summarized in Table 1. All the reports incriminated heparin in the development of the observed prothrombotic state. These patients received heparin for one of three reasons: (a) initial presentation with thrombosis; (b) increased risk of thrombo-embolism development due to an underlying medical condition, e.g. atrial fibrillation; (c) extracorporeal membrane oxygenation.

The commonest type of thrombosis observed was venous thrombosis, mimicking the pattern of thrombosis observed in recipients of ChAdOx vaccination, men were affected more than women (84% versus 16%), and median age was 58 years.

A rise in equivalent reports following ChAdOx vaccination indicates that heparin might not be the cause of this HIT-like syndrome after all. Instead, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could induce an autoantibody profile just like that of HIT (see Fig. 1).

Why is the prothrombotic thrombocytopenic disorder observed mainly with ChAdOx vaccine and not with other vaccines?

It remains unclear why the HIT-like syndrome is observed mainly with the ChAdOx vaccine and not with other coronavirus disease 2019 (COVID-19) vaccines. A possible explanation was given by Othman et al. [13], who confirmed the occurrence of persistent unexplained thrombocytopenia and platelet dysfunction with vaccines that use adenoviruses as viral vectors. This might signify that adenoviruses can synergize with SARS-CoV-2 antigens in inducing the autoantibodies causing such prothrombotic thrombocytopenic disorders. This indicates that all other COVID-19 vaccines using the same technology may cause the same complication. This is yet to be determined.

### Diagnostic and therapeutic implications

These findings necessitate updating laboratory testing and treatment of individuals with COVID-19 presenting with thrombosis, through the following protocol.

#### Routine anti-PF4 testing

The high prevalence of anti-PF4 in individuals with COVID-19 previously diagnosed with HIT (as mentioned in Table 1) warrants screening of this antibody profile in individuals presenting with thrombotic events, both COVID-19 patients and individuals after ChAdOx vaccination.

#### Alternative anti-coagulants

Three non-heparin anticoagulants, namely danaparoid, lepirudin and argatroban, are used in HIT as alternative anticoagulants because they do not cross-react with HIT antibodies. Similarly, low-molecular-weight heparin should not be used in individuals with COVID-19 and in ChAdOx-vaccinated individuals because

| Authors          | Country of authors | Age in years | Sex | Type of prothrombotic state                                      |
|------------------|--------------------|--------------|-----|----------------------------------------------------------------|
| Madala et al. [4]| USA                | 65           | Female | Lacunar infarct in basal ganglia and right-sided hemiplegia  |
| Kewen et al. [5] | USA                | 56           | Male  | DVT                                                              |
| Lingamani et al. [6] | USA     | 63           | Male  | DVT                                                              |
| Sartori et al. [7]| Italy             | 78           | Male  | DVT                                                              |
| Bidar et al. [8] | France            | 62           | Female | Pulmonary embolism                                              |
| Ogawa et al. [9] | Japan             | 38           | Male  | Deteriorating oxygenation                                        |
| Daviet et al. [10]| France            | 46           | Male  | DVT, massive pulmonary thromboembolism                          |
| Ogawa et al. [9] | Japan             | 50           | Male  | Intracardiac thrombosis                                         |
| Phan et al. [12] | Vietnam           | 43           | Male  | DVT/Pulmonary micro-thrombi, deteriorating oxygenation          |
| Lezcano and Franco [11] | Spain        | 45           | Male  | None                                                             |
|                  |                   | 71           | Male  |                                                                  |
|                  |                   | 90           | Male  |                                                                  |
| Summary          | Maximum age: 90 years | Minimum age: 37 years | Median age: 58 years | 13 presented with thrombotic events (72%) | DVT/pulmonary embolism: commonest prothrombotic event (9 cases/61%) |
|                  |                    |              |       | Total of 18 cases                                               |

Abbreviations: COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis.
of its cross-reactivity with PF4 autoantibodies. Warfarin is also discouraged in HIT because of a paradoxical increase in the thrombotic tendency.

On the other hand, high-dose intravenous immunoglobulins are one of the best-established therapies for HIT.

A final therapeutic approach of importance is using heparin-like molecules to disrupt the PF4–glycosaminoglycan complexes. This is considered in the treatment of HIT and could be regarded as a treatment for the prothrombotic state in individuals with COVID-19 and in ChAdOx-vaccinated individuals [14].

Vaccination of recipients of warfarin and heparin-based anticoagulants

A final aspect learnt from the observed prothrombotic syndrome is the choice of a suitable COVID-19 vaccine in those receiving heparin-based anticoagulants or warfarin. Caution should be exercised on administering adenovirus-mediated viral vector vaccines, such as ChAdOx, because of the ability of those medications to induce the same autoimmune complication.

Conclusion

Increasing evidence suggests that SARS-CoV-2 is an independent risk factor for PF4 autoantibody development, regardless of previous heparin therapy. The reports encountered following ChAdOx vaccination and SARS-CoV-2 infection advocate for this hypothesis. This information warrants clinicians to screen for specific autoantibodies in any individual with COVID-19 and in ChAdOx-vaccinated individuals presenting with a thrombotic event. It may also lead to advances in the anti-coagulant regimens and treatments used in these patients; such as avoidance of heparin-based anticoagulants and the use of immunoglobulins and Hep-like molecules that can disrupt PF4–glycosaminoglycan complexes. Finally, yet importantly, the autoimmune reaction observed with ChAdOx vaccine, might not only be mediated by SARS-CoV-2 antigens but also by the adenovirus used as a vector for this vaccine. Recipients of similar vaccines using the same technology should therefore be followed up for similar thrombotic thrombocytopenic events.

Conflict of interest

The authors declare that they have no financial links with any of the suppliers of the suggested alternative anticoagulants.

Acknowledgements

We want to thank every front-liner in all medical facilities around the world, they have helped many of us to preserve their loved ones, sometimes at the expense of their own lives.
As a first author, I wanted to thank the wonderful families of my students who co-authored with me, this work as well as many of my previous works. The authors would like to thank their wonderful colleague and great graphic designer Nadine El-Husseiny who provides us with her artwork to enrich our publications. Finally, yet importantly, we would like to express our gratitude to four of our best colleagues, namely, Peter Afdal, Rahma Menshawey, Esraa Menshawey and Mariem Arsanyous for their great input in all our previous works.

References

[1] Guerstein S, Romeo-Aznar V, Dekel M, Miron O, Davidovitch N, Puzis R, et al. Optimal strategies for combining vaccine prioritization and social distancing to reduce hospitalizations and mitigate COVID19 progression. medRxiv 2020. https://doi.org/10.1101/2020.12.22.20248622. Preprint from.

[2] Sweden joins Germany, France, and 15 other countries in suspending AstraZeneca’s vaccine over possible side effects [Internet]. Available at: https://www.businessinsider.com/astrazeneca-covid-vaccine-countries-suspend-denmark-thailand-batch-blood-clots-2021-3.

[3] Greinacher A, Thiele T, Warkentin TE, Weisser K. A prothrombotic thrombocytopenic disorder resembling heparin-induced thrombocytopenia following coronavirus-19 vaccination. Res Square 2020. https://doi.org/10.21203/rs.3.rs-362354v1. Preprint from.

[4] Madala S, Krzyzak M, Dehghani S. Is COVID-19 an independent risk factor for heparin-induced thrombocytopenia? Cureus 2021;13:1–8.

[5] Kewan T, Covut F, Dhw H, Haddad A. Heparin-induced thrombocytopenia in a patient with coronavirus disease-19. Am J Ther 2020. epub ahead of print.

[6] Lingamaneni P, Gonakoti S, Moturi K, Vohra I, Zia M. Heparin-induced thrombocytopenia in COVID-19. J Investig Med High Impact Case Rep 2020;8:4–7.

[7] Sartori M, Cosmi B. Heparin-induced thrombocytopenia and COVID-19. Hematol Rep 2021;13(1). Mar 12.

[8] Bidar F, Hékimian G, Martin-Toutain I, Lebreton G, Combes A, Frère C. Heparin-induced thrombocytopenia in COVID-19 patients with severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation: two case reports. J Artif Organs 2020 Aug 12. in press.

[9] Ogawa Y, Nagata T, Akiyama T, Nishida K, Kumazawa J, Kohno M, et al. Argatroban therapy for heparin-induced thrombocytopenia in a patient with coronavirus disease 2019. J Thromb Thrombolysis 2020;50:1012–4.

[10] Daviet F, Guervilly C, Baldesi O, Bernard-Guervilly F, Pilarczyk E, Genin A, et al. Heparin-induced thrombocytopenia in severe COVID-19. Circulation 2020;142:1875–7.

[11] Lozano R, Franco ME. Incidence of heparin-induced thrombocytopenia in patients with 2019 coronavirus disease. Med Clin (Barc) 2020;155:409–10.

[12] Phan XT, Nguyen TH, Tran TT, Huynh THT, Hoang TH, Nguyen VCV, et al. Suspected heparin-induced thrombocytopenia in a COVID-19 patient on extracorporeal membrane oxygenation support: a case report. Thromb J 2020;18:1–5.

[13] Othman M, Labelle A, Mazzetti I, Elbatarny HS, Lillicrap D. Adenovirus-induced thrombocytopenia: the role of von Willebrand factor and P-selectin in mediating accelerated platelet clearance. Blood 2007;109:2832–9.

[14] Alkindi S, Smith OP, Enright H. Successful use of alternative anticoagulants in the management of heparin-induced thrombocytopenia with thrombotic complications: report of 5 cases and review of literature. Sultan Qaboos Univ Med J 2011;11:391–8.

© 2021 The Author(s). Published by Elsevier Ltd. NMNI, 41, 100884
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).