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COVID-19 VACCINES AND CEREBRAL VENOUS THROMBOSIS

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Today, we are witnessing the deadliest pandemic of our time. As of May 25 2021, over 167 million people have been affected with the coronavirus disease 2019 (COVID-19) globally with approximately 3.5 million confirmed deaths.[1] Among the catastrophe, the COVID-19 preventive vaccinations have been a ray of hope. The World Health Organization (WHO) approved Comirnaty (Pfizer/BioNTech) as the first COVID-19 vaccine for emergency use on 31 December 2020. The list has been updated with six more vaccines till now; Oxford-AstraZeneca, Janssen (Johnson & Johnson), AstraZeneca-SK Bio, Covishield, Moderna, and recently, Sinopharm.[2] Comirnaty (Pfizer/BioNTech) and Moderna are modified mRNA-based vaccines. Oxford-AstraZeneca and Janssen use a recombinant adenoviral vector encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein. The AstraZeneca-SK Bio and Covishield are basically the versions of Oxford-AstraZeneca that are manufactured in South Korea and India, respectively, using the same techniques. Sinopharm vaccine uses an inactivated SARS-COV-2 virus. Vaccine efficacy to prevent symptomatic COVID-19 disease ranges from 65 - 95% [3] and over 1.7 billion vaccine doses have so far been administered.[1]

Since the vaccines have been fast-tracked for emergency use, the short and long-term safety profile has been a point of concern. These concerns escalated when multiple cases of thromboembolism along with thrombocytopenia were initially reported in AstraZeneca (AZ) vaccine recipients in early March 2021, which led to a temporary suspension of the AZ vaccination in European countries for further investigation.[4] An initial study reported 11 patients (82% females) with thromboembolic complications after the AZ vaccine. The majority of them had cerebral venous thrombosis (CVT) (82%; n=9) followed by splanchnic vein and pulmonary thrombosis (n=3 each). Some patients experienced >1 thrombotic event.[5] Besides AZ, Jannsen recipients also developed rare thrombosis and thrombocytopenia. Janssen vaccine was briefly suspended on 10 April 2021 when 6 persons out of 6.8 million doses of Janssen vaccine developed CVT along with thrombocytopenia. After two weeks, the U.S. Food and Drug Administration (FDA) resumed the Janssen use labeling the vaccine-induced thrombotic thrombocytopenia (VITT), also called thrombosis with thrombocytopenia syndrome (TTS), as its rare adverse effect. As of April 23, 2021, only 15 cases of VITT/TTS were reported after the Janssen vaccine. Interestingly, all of these cases occurred in young women with a median age of 37 years and within two weeks post-vaccination.[6]

A binational population-based study from Denmark and Norway analyzed the rates of thrombosis within the 28-day period post-AZ vaccination (n= 281,264). They concluded a higher rate of venous thromboembolism corresponding to a standardized morbidity ratio (SMT) of 1.97 (95% CI, 1.50 – 2.54) and 11 excess venous thromboembolic events per 100,000 vaccinations as compared to the general population. A clear higher rate of CVT was, however, reported with an SMT of 20.25 (95% CI, 8.14 – 41.73) and 2.5 excess events per 100,000 vaccinations. No increase in arterial thromboembolic events was reported with SMT of 0.97 (95% CI, 0.77 – 1.20) but a higher SMT of 2.33 (95% CI; 1.01 – 4.59) for intracerebral hemorrhage was seen.[3]

CVT after COVID-19 vaccines is presumed to be due to immune response to platelet factor 4 (PF4). This is supported by the presence of platelet-activating antibodies as well as strong reactivity of post-vaccine CVT patients' sera in anti-PF4/heparin enzyme immunoassay. The pathogenesis is similar to heparin-induced thrombocytopenia (HIT), which is a prothrombotic disorder and consumes platelets causing thrombocytopenia.[7] The only difference is that most of the persons with VITT have no previous history of heparin use and the immune-triggering factor is supposed to be something else, albeit still relatively unknown. In recent years, multiple triggers other than heparin have been recognized that may cause a prothrombotic disorder, similar to HIT. These triggers include various polyanionic compounds (e.g., pentosanpolysulfate), hypersulfated chondroitin sulfate, infections, or certain procedures, for instance, total knee arthroplasty.[8]

CVT, on other hand, is also reported in COVID-19 patients, presumably due to a hypercoagulable state.[9,10] A retrospective cohort study from the United States (US), available as a non-peer-reviewed preprint, reported a higher CVT incidence of 39.0 per million COVID-19 patients (n=513,284) as compared to 0.41 per million in general population and 4.1 per million who received vaccination (RR 6.36, P<0.001). Vaccine recipients in this study had an mRNA vaccine, either Pfizer-BioNTech or Moderna, since AstraZeneca is not available in the US. The authors concluded that the risk of CVT after COVID-19 is approximately 8-10 times higher than reported for the vaccines, and about 100-fold higher than the general population.[11] An estimated risk of CVT after the AZ vaccine is reported to be 2.6 cases per million people in UK over the 4-month period (62 CVT cases among the near 25 million people vaccinated).[12] With the number of reported post-vaccination CVT cases with AZ, the CVT incidence rate of 2.6 (compared to 4.1 with Pfizer and Moderna vaccines[11] seems an understatement. The other possibility is of observational (detection) bias. The level of attention given to the sporadic CVT cases in vaccine-recipients is many times higher than given to the routine CVT cases in daily practice, giving an impression of increased numbers.[12] Although for rare events and cross-sectional studies, a cause-and-effect relationship cannot be easily assessed, an increased CVT reporting in recipients of AZ and Janssen vaccines along with the almost total absence of cases after Pfizer, Moderna, or Sinopharm vaccines is something to look for. Additional findings of thrombocytopenia, which is not normally found in CVT patients, also hints towards a possible association.

Recognition of VITT/TTS has certain important clinical and epidemiological implications. First, healthcare workers should be aware that the onset of thrombosis, particularly CVT, may occur up to two weeks post-vaccination for timely diagnosis and management. To date, this has only been reported with the AZ and Janssen vaccines. Second, HIT enzyme immunoassays may be used to investigate potential anti-PF4 antibody-associated VITT/TTS. Third, due to the lack of available data, the safety and efficacy of heparin in VITT/TTS is not known. Use of non-heparin anticoagulants (e.g. rivaroxaban, apixaban) is recommended. Intravenous immune globulin may also be used in severe cases. Fourth, the risk of CVT in COVID-19 patients is many folds higher than with vaccination, albeit the association with the later still need to be ascertained, and the vaccines are our main tools to control this deadly pandemic. Fifth, the main similarity between AZ and Janssen is the use of a recombinant adenoviral vector as a transport medium to deliver the genetic material of SARS-CoV-2 spike protein to human cells to trigger an immune response. The question of whether the rare occurrence of VITT/TTS is related to adenoviral vector is still elusive and needs further research. Data of other COVID-19 vector-vaccines pending WHO approval, for instance, Russian Sputnik V or Chinese CanSino vaccine, should be carefully analyzed for thromboembolic events and thrombocytopenia.

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