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Letter to the Editor

Oxford-AstraZeneca COVID-19 vaccine-induced cerebral venous thrombosis and thrombocytopaenia: A missed opportunity for a rapid return of experience

Dear Editor,

Oxford-AstraZeneca COVID-19 vaccination started In France the 6th of February 2021, with 3.7 million doses being administered on the 25th of April 2021. The 21st and 23rd of March 2021, we had to manage in the ICU two patients with severe cerebral venous thrombosis associated with thrombocytopaenia in the context of recent vaccination. Progressive severe disorders of consciousness developed and decompressive craniectomy was performed in both patients.

We were aware of the possibility of cerebral venous thrombosis after COVID-19 vaccination, and the declaration to our regional pharmacovigilance centre was made on the 23rd of March 2021. We would like, however, to share the difficulties we had to find reliable clinical information in this context.

Our knowledge of the pathophysiology and therapeutic possibilities was very limited. Several major issues were questioned as the performances of detection methods for antibodies against platelet factor 4 (PF4)/heparin complex, possible efficacy of steroids, intravenous immunoglobulins, plasma exchange, or choice of anticoagulants.

A search on PubMed database on the 22nd and 23rd of March 2021 did not find any relevant publications. A Google search found a release from a German group on the subject (first in German language on the 19th of March, and secondly in English language on the 22nd of March 2021) (https://gth-online.org/wpcontent/uploads/2021/03/GTH_Stellungnahme_AstraZeneca_engl._3_22_2021.pdf). Based on case series, the GTH (Gesellschaft für Thrombose- und Hämostaseforschung, Germany) proposed a diagnosis algorithm for screening test based on "immunological detection of antibodies against the platelet factor 4 (PF4)/heparin complex. In case this test is negative, a heparin-induced thrombocytopaenia (HIT)-like specific immunological cause of thrombosis/thrombocytopaenia can be ruled out… and critical thromboses such as sinus/cerebral or splanchnic vein thrombosis, the prothrombotic pathomechanism can very likely be interrupted by the administration of high-dose intravenous immunoglobulins… "

This was the only reliable information we had at this time. Without information and feedback from similar cases, we felt like engaging in shady dealings without really understanding the pathophysiological processes of the disease and the risks/benefits balance of therapeutic options.

In the first days of the management of these patients, we organised videoconference meetings with the local and national experts (vascular neurologists, neurointensivists, neuroradiologists, haemostasis specialists, internal medicine and virologists) sharing the knowledge and the possible cases occurring in France and around the world.

In our two patients, the anti-PF4 antibodies were negative (Latex Immunoturbidimetric Assay HemosIL® HIT-Ab (PF4-H) performed using the ACL TOP® instrument). Despite early and aggressive treatment of these two cases of severe cerebral venous thrombosis, the medical management of anticoagulant therapy and thrombocytopaenia in this specific post-vaccination context was complex. The predominantly thrombotic clinical expression and the absence of anti-PF4 antibodies, which could have been evidence of spontaneous heparin-induced thrombocytopaenia, led to consider that thrombocytopaenia was of autoimmune mechanism that may be induced by vaccine. Thrombotic anti-phospholipid syndrome was ruled out in both patients by negative testing for Lupus anticoagulants, anticardiolipin antibodies (ELISA), and anti-β2-glycoprotein I antibodies in plasma. The JAK2 V617F mutation was not present. Paroxysmal nocturnal haemoglobinuria was ruled out in both patients by absence of haemolytic anaemia and normal levels of bilirubin, haptoglobin and reticulocytes.

In the hypothesis of immunological thrombocytopaenia, heparin was continued and associated with corticosteroids followed by intravenous immunoglobulins in one patient. Later, we had the confirmation of a definite case of a Vaccine-induced Immune cerebral venous Thrombosis and Thrombocytopaenia (VITT syndrome) with the help of an expert laboratory and the detection of significant levels of IgG antibodies to PF4 by ELISA when the samples were analysed with the method using polyvinylsulfonate-PF4 (LIFECODES PF4 IgG, Immucor®) and with strong platelet activation confirmed by a sensitised PF4-supplemented Serotonin Release Assay [1].

Unfortunately, both patients had unfavourable outcome with refractory intracranial hypertension leading to death. More than 10 days after the death of our two patients, cases of VITT were published online on the 9th and 16th of April 2021 [2–4], representing a total of 39 cases. Guidance produced from the Expert Haematology Panel (UK) for the diagnosis and management of VITT was released online on the 1st of April 2021 (https://b-s-h.org.uk/about-us/news/covid-19-updates/). We participated in the production of French Guidance published on the 2nd of April 2021 (https://site.geht.org/app/uploads/2021/04/prise-en-charge-en-urgence-TVC-contexte-vaccination-anticovid-SFNV-SFMV-GFHT-V2-02042021.pdf). Both publications highlighted the poor performances of rapid anti-PF4 antibodies detection in this context.

We retrospectively performed an analysis of the reports of venous embolic or thromboembolic reports with thrombocytopaenia after AstraZeneca COVID-19 vaccine recorded in VigiBase® (Word Health Organization pharmacovigilance database). Between the 1st of February and the 23rd of April 2021, 298 cases were reported (no cases recorded in January), coming from UK, Germany, Spain, Italy, France, Netherlands, Austria, Norway, Australia, Finland, Sweden, Belgium, Hungary, Latvia, North Macedonia and Poland. Sixty-one per cent were reported by UK. Interestingly, 67 cases (22%) were registered to pharmacovigilance

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