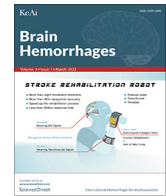




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Apropos of menstrual changes and abnormal uterine bleeding after COVID-19 vaccination

Luca Roncati*, Antonio Manenti

Department of Surgery, Medicine, Dentistry and Morphological Sciences with interest in Transplantation, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy

ARTICLE INFO

Article history:

Received 1 November 2022

Accepted 3 November 2022

Available online xxxx

Keywords:

Coronavirus disease 2019 (COVID-19)

Severe acute respiratory syndrome coronavirus 2 (SARS CoV 2)

COVID-19 vaccination

Menstrual changes

Heavy menstrual bleeding

Abnormal uterine bleeding

Adenohypophysis microcirculation

Fenestrated capillaries

ABSTRACT

It is news of 28 October 2022 that the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency has recommended to add heavy menstrual bleeding among the side effects of unknown frequency inside the package insert of nucleoside-modified messenger ribonucleic acid vaccines to prevent coronavirus disease 2019 (COVID-19). The decision has been made in the light of the numerous reports of unexpected menstrual changes or abnormal uterine bleeding following COVID-19 vaccination. Here we advance a possible involvement of the particular adenohypophyseal microcirculation in these strange and still unexplained events.

© 2022 International Hemorrhagic Stroke Association. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

It is news of 28 October 2022 that the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended to add heavy menstrual bleeding among the side effects of unknown frequency inside the package insert of nucleoside-modified messenger ribonucleic acid (modRNA) vaccines to prevent coronavirus disease 2019 (COVID-19), the ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{1–2} Previously, we have pointed out the numerous reports of unexpected menstrual changes or abnormal uterine bleeding following COVID-19 vaccination recorded on the United Kingdom “Yellow Card” surveillance system.³ In this regard, we have described a similar case of amenorrhea due to hyperprolactinemia in a 28-year-old Caucasian female with pituitary apoplexy (PA) accompanied by *de novo* headache, temporally after adenoviral vector-based COVID-19 vaccination.³ To complete this clinical case, we here specify the full absence of SARS-CoV-2 infec-

Abbreviations: PRAC, Pharmacovigilance Risk Assessment Committee; EMA, European Medicines Agency; modRNA, nucleoside-modified messenger ribonucleic acid; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PA, pituitary apoplexy; CD31, cluster of differentiation 31.

* Corresponding author at: Largo del Pozzo 71, Polyclinic Hospital (Pavilion 26), 41124 Modena, Emilia-Romagna, Italy.

E-mail addresses: luca.roncati@unimore.it, roncati.luca@aou.mo.it, emailmedica@gmail.com (L. Roncati).

<https://doi.org/10.1016/j.hest.2022.11.001>

2589-238X/© 2022 International Hemorrhagic Stroke Association. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please cite this article as: L. Roncati and A. Manenti, Apropos of menstrual changes and abnormal uterine bleeding after COVID-19 vaccination, Brain Hemorrhages, <https://doi.org/10.1016/j.hest.2022.11.001>

tion by molecular swab, of visual disturbance by ophthalmologic investigation, of micro-/macroadenoma by cerebral imaging (performed only after the second dose when the patient came to our attention), and of cardiovascular risk factors, such as diabetes, arterial hypertension, hyperlipidemia, atrial fibrillation, smoking and anti-contraceptive pill. All these additional data allow us to advance a possible alternative explanation for PA and transient menstrual changes concerning with an acute microvascular damage. In fact, the particular microcirculatory apparatus of the adenohypophysis consists of a rich network of fenestrated capillaries which account for the high metabolic exchanges of the gland, strictly dependent on the hypothalamus by feedback mechanism [Fig. 1]. It is known that the main arterial supply for the adenohypophysis is represented by the two superior hypophyseal arteries; the branches of each artery terminate in a primary capillary plexus, which allows for the rapid passage of hypothalamic-releasing hormones and inhibitory factors into the hypophyseal portal system.^{4–5} Once the blood reaches the adenohypophysis, it spreads within a secondary capillary plexus precisely consisting of fenestrated capillaries, in direct contact with the secretory cells [Fig. 1]. The main venous return is towards the cavernous sinus, but supplementary collaterals are connected with the hypothalamus' basis, allowing a direct arrival of blood enriched with pituitary hormones to the hypothalamus.⁴ Given that COVID-19 can

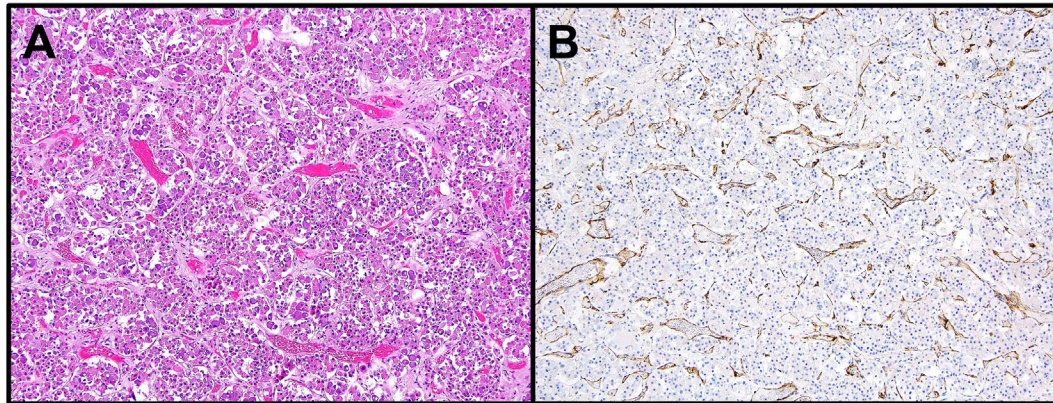


Fig. 1. Histology and immunohistochemistry of the adenohypophysis from an adult woman in course of autopsy: a rich network of capillaries in direct contact with the secretory cells is well noticeable (A, haematoxylin & eosin, 200X) and highlighted by the immunoreaction for the cluster of differentiation 31 (CD31), which specifically stains in brown the blood endothelia (B, JC70 clone, 200X).

rarely complicate with pituitary apoplexy and that any vaccination represents an attenuated form of the disease by definition,³ a resulting hypercoagulative state may rarely occur and involve fenestrated capillaries, where the blood flow is significantly decelerated.^{6–8} The pre-existing interconnected small branches and the *trans*-sellar arterial blood supply usually are sufficient collaterals,⁹ but sometimes they could be inadequate to the high blood demand from the pituitary gland, thus promoting the onset of microischemic events and subsequent menstrual abnormalities.¹⁰

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Statement of ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki of 1975, as revised in 2008.

Data availability statement

All relevant data generated or analyzed during this research were included in the article; further enquiries can be directed to the corresponding author upon reasonable request.

Author contributions

LR: study concept and design, image acquisition, drafting of the manuscript and caption, study supervision. AM: drafting of the manuscript, critical revision. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no competing interest.

Acknowledgments

The authors thank the neuropathologist Dr. Elena Zunarelli, MD for her help in retrieving the histological material.

References

1. European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 24–27 October 2022. Available online at: <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022> [last accessed October 28, 2022].
2. Roncati L, Corsi L. Nucleoside-modified messenger RNA COVID-19 vaccine platform. *J Med Virol.* 2021;93:4054–4057.
3. Roncati L, Manenti A. Pituitary apoplexy following adenoviral vector-based COVID-19 vaccination. *Brain Hemorrhages.* 2022. <https://doi.org/10.1016/j.hest.2022.04.002>.
4. Phelps C. The anterior pituitary and its hormones. In: Enna SJ, Bylund DB, eds. *XPharm: The Comprehensive Pharmacology Reference.* Elsevier; 2007:1–12.
5. Felten DL, O'Banion MK, Summo MM. Vasculature. In: Felten DL, O'Banion MK, Summo Maida M, eds. *Netter's Atlas of Neuroscience.* 3rd ed. Elsevier; 2016:93–124.
6. Roncati L, Ligabue G, Nasillo V, et al. A proof of evidence supporting abnormal immunothrombosis in severe COVID-19: naked megakaryocyte nuclei increase in the bone marrow and lungs of critically ill patients. *Platelets.* 2020;31:1085–1089.
7. Roncati L, Corsi L, Barbolini G. Abnormal immunothrombosis and lupus anticoagulant in a catastrophic COVID-19 recalling Asherson's syndrome. *J Thromb Thrombolysis.* 2021;52:1043–1046.
8. Roncati L, Manenti A, Manco G, Farinetti A, Mattioli A. The COVID-19 arterial thromboembolic complications: from inflammation to immunothrombosis through antiphospholipid autoantibodies. *Ann Vasc Surg.* 2021;72:216–217.
9. Spinelli CP, Iwanaga J, Hur MS, Dumont AS, Tubbs RS. Discovery of a *trans*-sellar vascular supply for the pituitary gland. *Anat Cell Biol.* 2022;55:124–129.
10. Roncati L, Manenti A, Corsi L. A three-case series of thrombotic deaths in patients over 50 with comorbidities temporarily after modRNA COVID-19 vaccination. *Pathogens.* 2022;11:435.