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.

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The importance of recognizing cerebral venous thrombosis following anti-COVID-19 vaccination

To the Editor.

In March 2021, the reporting of cases of thrombosis post-COVID-19 vaccine AstraZeneca raised safety concerns and determined the temporary suspension of vaccinations in some countries in Europe [1]. On the 18th of March, EMA published its preliminary review of cases concluding that "the benefit of the vaccine in combating the still widespread threat of COVID-19 (which itself results in clotting problems and may be fatal) continue to outweigh the risk of side effects" [2]. On the same day, a one-week campaign was launched in Italy through the secretariat of the Hospital Neurosciences Society (SNO) to gather all cases of cerebral venous thrombosis within one month of anti-COVID-19 vaccine administration. The purpose of this campaign is to identify, through an exhaustive collection of post-COVID-19 vaccine cerebral venous thrombosis cases, a common pattern among demographic, clinical, laboratory and risk factors, to support a possible causal link between COVID-19 vaccine and cerebral thrombosis.

The most remarkable findings of the cases observed (Table 1) are early platelet consumption (82%), extra-cerebral thrombosis (73%) and poor outcome (only one patient without neurological deficit) with high mortality (45%), compared to expected mortality of less than 5% in patients with cerebral sinus thrombosis not exposed to the COVID-19 vaccine [3]. Clinical manifestation appeared during the first 11 days after the vaccination.

These issues led to speculation that COVID-19 vaccine might determine cerebral venous thrombosis due to an immune thrombocytopenia [4] as described in SARS-CoV-2 infection, through molecular mimicry between virus and platelet antigens [5]. Similarly, after vaccination, the antibodies produced against the spike proteins might cross-react with specific antigens expressed on the platelet surface. The reason why such a chain of events sporadically occurs remains obscure.

Therefore, cerebral venous thrombosis after COVID-19 vaccination can be the first manifestation of a much more complex disorder mimicking heparin-induced thrombocytopenia. An inclusive awareness of the clinical and laboratory features of these events plays a crucial role in the early identification of patients at their first clinical manifestation, in order to undertake all the possible measures to prevent the dramatic consequences of immune thrombocytopenia. Although from these case series there is no evidence of any predisposing conditions to identify patients at risk, the widespread knowledge of this possible severe adverse event of COVID-19 vaccination is already a valid prevention strategy.

Declaration of Competing Interest

None.

Appendix

Italian working group on cerebral venous thrombosis after COVID-19 vaccination: Maria Pia Mazzaferro, MD, Roberto Acampora, MD, and Fabrizio Fasano, MD (Ospedale del Mare, ASL Napoli 1 Centro, Napoli); Carla Zanferrari, MD, Simona Fanucchi, MD, and Lucio Liberato, MD (Azienda Socio Sanitaria Territoriale Melegnano e Martesana); Paolo Candelaresi, MD, and Mario Muto, MD (Azienda Ospedaliera di Rilievo Nazionale Antonio Cardarelli, Napoli); Francesco Sica, MD, Fabrizia Monteleone, MD, and Maria Carmelina Costa, MD (Ospedale Santa Maria Goretti - ASL Latina); Rosa Musolino, MD, Francesco Grillo, MD, and Cristina Dell'Aere, MD (Policlinico Universitario Messina); Francesca Romana Pezzella, MD, PhD, BSc (Azienda Ospedaliera San Camillo Forlanini, Roma); Giovanni Frisullo, MD, Giacomo Della Marca, MD, and Anselmo Caricato, MD (Fondazione Policlinico Universitario Agostino Gemelli –IRCCS, Roma); Bruno Bonetti, MD, PhD, and Manuel Cappellari, MD (Azienda Ospedaliera Universitaria Integrata, Verona); Domenico Sergio Zimatore, MD, Luigi Chiumarulo, MD, and Alessandro Introna, MD (Azienda Ospedaliero Universitaria Consorziale Policlinico, Bari); Florindo d'Onofrio, MD, Daniele Spitaleri, MD, and Elisabetta Iannaccone, MD (Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati, Avellino); Renato Gigli, MD (UPMC Salvator Mundi International Hospital, Roma).

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Table 1
Characteristics of patients with cerebral vein thrombosis following COVID-19 vaccine. We considered the day of vaccination as day 0.

Patient No.	Sex	Age (yrs)	Type of vaccine	Risk factors	Onset of neurological symptoms	Cerebral vein involved	Type of cerebral damage	Extracerebral thrombosis	No. of platelets ($*10^3$/uL) upon first admission to the hospital	I.N.R, aPTT ratio	D-Dimer (ng/mL)	Treatments	Outcome
1	M	50	AstraZeneca, first dose	Smoker	Headache on day 7	Superior sagittal, left straight and sigmoid sinuses, gulf of the jugular vein	Massive brain hemorrhage with trans-tentorial herniation	Pulmonary embolism	15	1.19, 0.88	>10000	S.c. enoxaparin, i.v. mannitol, craniectomy	Death on day 13
2	F	42	AstraZeneca, first dose	Mutation factor II	Headache, fever on day 0	Superior sagittal, right straight and sigmoid sinuses, gulf of the jugular vein	Brain hemorrhagic infarction	Suprahepatic vein	59	1,31, 0.9	31458	S.c. enoxaparin, i.v. mannitol, thrombectomy, craniectomy.	In a coma on day 23
3	F	55	Pfizer, second dose	Obesity	Headache on day 1	Right straight and sigmoid sinuses, jugular vein	Brain hemorrhage	Suspected pulmonary embolism	59	1.33 0.83	9000	S.c. enoxaparin	Death on day 5
4	F	32	AstraZeneca, first dose	Thrombocytopenia in infancy with brain hemorrhage, oral contraceptive	Headache, orbital bruising, abdominal pain and fever, on day 1	Left straight and sigmoid sinuses	Cerebella hemorrhagic infarction with tonsillar herniation	Epigastric and periuterin veins thrombosis, renal infarction	30	1.28, 1.14	11332	Fondaparinux, metil-prednisolon	Death on day 24
5	F	35	AstraZeneca, first dose	Oral contraceptive	Headache, nausea and vomiting on day 6	Superior sagittal, right straight and sigmoid sinuses	Brain hemorrhagic infarction with and midline shift	Portal and mesenteric veins	44	1.03 0.86	>8000	I.v. mannitol, i.v. metil-prednisolon, i.v. fresh plasma, c. c. enoxaparin, plasmapheresis	In a coma on day 13
6	F	51	AstraZeneca, first dose	Heterozygosis for factor V Leiden and MTHFR	Headache, vomiting and drowsiness on day 10	Left straight and sigmoid sinuses, jugular vein, Galeno and internal cerebral veins	Bilateral deep brain hemorrhagic infarction with brain swelling	Pelvic district.	50	1.14 0.83,	35200	I.v. remifentanil and noradrenalin, ventriculostomy	Death on day 13
7	M	64	AstraZeneca, first dose	Sinusitis	Headache and vomiting on day 4	inferior sagittal, anterior part of the superior sagittal, left straight and sigmoid sinuses	None	None	187	NA, 1.03	2500	S.c. enoxaparin	No neurological deficit on day 20
8	F	40	AstraZeneca, first dose	Anamnestic spontaneous abortion	Headache on day 5	Inferior sagittal, left straight and sigmoid	Brain hemorrhagic infarction	Brain hemorrhagic infarction	40	1.06 0.82,	27546	S.c. fondaparinux	Aphasia and right hemiparesis on day 15

(*continued on next page*)

Table 1 (*continued*)

Patient No.	Sex	Age (yrs)	Type of vaccine	Risk factors	Onset of neurological symptoms	Cerebral vein involved	Type of cerebral damage	Extracerebral thrombosis	No. of platelets ($*10^3$/uL) upon first admission to the hospital	I.N.R, aPTT ratio	D-Dimer (ng/mL)	Treatments	Outcome
						sinuses and jugular vein							
9	F	49	AstraZeneca, first dose	Contraceptive vaginal ring, migraine with aura	Headache on day 11	Left straight and sigmoid sinuses, jugular vein	Brain hemorrhagic infarction with swelling	None	278	0.96 0.73	14700	S.c. enoxaparin, i.v. mannitol	Significant disability at day 20
10	F	54	AstraZeneca, first dose	None	Headache and vomiting on day 2	Superior sagittal sinus, Galen vein.	Brain hemorrhagic infarction, subarachnoid hemorrhage, brainstem infarction and swelling	Aortic arch, thoracic aorta, portal, suprahepatic, right coronary, pulmonary and basilar arteries	13	1.3 0.83	78254	S.c. enoxaparin, s.c. fondaparinux, desametasone	Death on day 15
11	F	55	AstraZeneca, first dose	None	Headache and fever on day 6	Left jugular vein	Cerebellar hemorrhagic infarction with swelling	Pulmonary thromboembolism, portal vein and inferior cava	31	1.34 0.92,	>10000	S.c. fondaparinux, i. v. metil-prednisolone, i.v. mannitol, craniectomy	In a coma on day 25

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Alfonso Ciccone*, Bruno Zanotti, The working group on cerebral venous thrombosis after COVID-19 vaccination[1]

Department of Neurology with neurosurgical activity and stroke unit, ASST di Mantova, Mantova, Italy

* Corresponding author at: Department of Neurology with neurosurgical activity and stroke unit, ASST di Mantova, Strada Lago Paiolo 10, 46100 Mantova, Italy.

E-mail address: alfonso.ciccone@asst-mantova.it (A. Ciccone).

[1] The list of the working group is in the Appendix.