Fatal intracerebral haemorrhage associated with thrombosis with thrombocytopenia syndrome after ChAdOx1-S vaccine

Ana Gómez-Roldós, Miguel González-Sánchez, Marta Vales-Montero, Pilar Vázquez-Alen, Yolanda Fernández-Bullido, Ana M. Iglesias-Mohedano, Fernando Díaz-Otero, Andrés García-Pastor, Antonio Gil-Núñez

Introduction. The COVID-19 pandemic has had a devastating impact on health, society and economics worldwide. Therefore, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have recently emerged as an important measure to fight the pandemic. ChAdOx1-S (Oxford-AstraZeneca) is an adenovirus-vectored vaccine that expresses the SARS-CoV-2 spike protein. It shows an acceptable safety profile. Nevertheless, several cases of unusual thrombosis and thrombocytopenia have been reported after initial vaccination with ChAdOx1-S mimicking autoimmune heparin-induced thrombocytopenia. This condition has been called thrombosis with thrombocytopenia syndrome (TTS) and complications such as intracerebral haemorrhage have been described.

Case report. We present a case of intracerebral haemorrhage after ChAdOx1-S vaccination. Middle-aged patient with no prior medical history was seen in the emergency room 16 days after the first dose of ChAdOx1-S vaccine with sudden onset left hemiplegia and severe holocranial oppressive headache. She did not receive heparin treatment in the previous 100 days. Blood test showed moderate thrombocytopenia and a right frontal lobar haemorrhage was seen on computed tomography scan, computed tomography venography was negative for thrombosis. The presence of antibodies against platelet factor 4 was confirmed. The patient's neurological condition progressively worsened. She developed a treatment resistant intracranial hypertension syndrome and she died three weeks later.

Conclusions. TTS is a rare adverse effect of ChAdOx1-S vaccine, defined by the presence of thrombosis in uncommon locations. In our case we report an spontaneous intracerebral haemorrhage probable due to the thrombocytopenia related to probable TTS. It represents a rare clinical presentation of TTS.

Key words. Autoimmune thrombocytopenia. Cerebrovascular accident. ChAdOx1-S vaccine. COVID-19 vaccine. Intracerebral haemorrhage. Thrombosis with thrombocytopenia syndrome (TTS).

Vascular Neurology Section and Stroke Center. Department of Neurology. Gregorio Marañón Health Research Institute-IiSGM. Hospital General Universitario Gregorio Marañón-Universidad Complutense de Madrid. Madrid, Spain (A. Gómez-Roldós, M. González-Sánchez, M. Vales-Montero, P. Vázquez-Alen, Y. Fernández-Bullido, A.M. Iglesias-Mohedano, F. Díaz-Otero, A. García-Pastor, A. Gil-Núñez).

Correspondence:
Dra. Ana Gómez-Roldos. Calle del Doctor Esquerdo, 46. E-28007 Madrid.

E-mail:
ana.roldos@gmail.com

Acknowledgements:
Thanks for their collaboration to the Hematology Service Hospital General Universitario Gregorio Marañón.

Accepted:
04.03.22.

Conflict of interests:
The authors declare no conflicts of interest.

How to cite this article:
Gómez-Roldós A, González-Sánchez M, Vales M, Vázquez-Alén P, Fernández-Bullido Y, Iglesias-Mohedano AM, et al. Fatal intracerebral haemorrhage associated with thrombosis with thrombocytopenia syndrome after ChAdOx1-S vaccine. Rev Neurol 2022; 75: 199-202. doi: 10.33588/rn.7507.2021323.

Versión española disponible en www.neurologia.com

© 2022 Revista de Neurología

Introduction

COVID-19 was recognized as a pandemic by the World Health Organization (WHO) on March 11th, 2020 [1]. Since then, the disease has increased morbidity and mortality worldwide. As a prevention strategy, several vaccines have been developed, including ChAdOx1-S from the AstraZeneca company [2]. This vaccine uses the modified chimpanzee adenovirus ChAdOx1 as a vector and has shown a success rate of 81.3% in preventing symptomatic SARS-CoV-2 infection after the second dose [3].

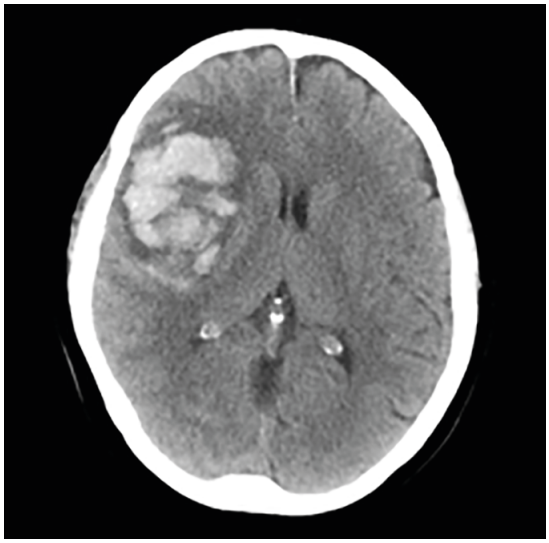
Following the vaccination of more than 400 million people, the profile of the vaccines has been found to be safe with a low risk of serious adverse effects. Within 3 to 30 days following vaccination with COVID-19 non-replicant adenovirus vector-based vaccines the thrombosis with thrombocytopenia syndrome (TTS) has been reported as a rare adverse effect with a cumulative incidence that ranges from 0.5 to 6.8 cases per 100,000 vaccinees [1].

The syndrome is defined by the presence of a thrombosis/thromboembolism in uncommon locations and marked thrombocytopenia mimicking heparin-induced immune thrombocytopenia's, since in most cases high levels of anti-platelet factor 4 antibodies (PF4) have been identified by enzyme-linked immunosorbent assay (ELISA) [4,5]. We report a case of intracerebral haemorrhage as a rare adverse event after ChAdOx1-S vaccination [6].

Case report

A female at around 60 years of age was admitted to the emergency department on April 27th, 2021, with sudden onset left hemiplegia and severe holo-

Figure. Computed tomography scan without contrast that shows a right frontal lobar haemorrhage (4 cm). Centered midline, no criteria of intracranial hypertension.



cranial oppressive headache of sudden onset in the last two hours. She had no history of vascular risk factors, cardiac or renal disease. The absence of heparin therapy within the prior 100 days was confirmed. First dose of the ChAdOx1-S vaccine was administered 16 days ago. The physical examination showed a blood pressure of 120/80 mmHg. Initially the patient was alert but with moderate dysarthria, left hemiplegia and forced ocular deviation to the right scoring 16 in the National institute of Health Stroke Scale (NIHSS).

An urgent cranial computed tomography scan showed a right frontal lobe haemorrhage without intracranial hypertension signs (Figure), computed tomography angiography did not reveal vascular anomalies underlying the hematoma. Neither were signs of visible cerebral vein thrombosis on computed tomography venography. Blood test showed a moderate thrombopenia 51,000/μL (references: 140,000-400,000/μL), with reference values of haemoglobin and leukocytes. The coagulation lab results only showed high levels of D-dimer 2,317 ng/mL (references: 0-250 ng/mL). In the biochemical analysis just a slight elevation of alanine transaminase (114 U/L; references: 5-31 U/L) and aspartate transaminase (56 U/L; references: 10-31 U/L) was found. Ions, renal profile and cardiac markers were on range. Urinary screening for drugs was negative. The patient had prior normal values of hematologic and coagulation parameters in tests performed at our center during the last five years. She had not received treatment with heparin or other drugs prior to admission.

The patient's level of consciousness deteriorated in the following two hours with an absence of ocular and verbal responses and flexion of right limbs at painful stimuli scoring 6 in Glasgow Coma Scale. As a result, she was evaluated by neurosurgeons and intensive care unit physicians. The neurosurgeons decided to drain the hematoma. No vascular anomalies were observed during the surgery. A platelet concentrate transfusion was required for the procedure. Subsequently, she was admitted to the intensive care unit where a control computed tomography scan after surgery showed signs of rebleeding as well as uncal and subfalcial herniation. Blood pressure values stayed below 120/80 mmHg. Computed tomography angiography and venography was repeated after surgery with no evidence of vascular anomalies nor cerebral vein thrombosis.

A progression in the thrombocytopenia and an increase of D-dimer was observed in the control blood tests that showed severe thrombopenia (19,000/μL; references: 140,000-400,000/μL) and higher levels of D-dimer (3,840 ng/mL; references: 0-250 ng/mL). Conversely, no data of disseminated intravascular coagulation were found. These tests did not indicate a disseminated intravascular coagulation. Anti-platelet factor 4 antibodies (PF4) were detected with ELISA technique suggesting a possible TTS which was confirmed with heparin-induced platelet activation. Therefore, treatment with intravenous immunoglobulins from day 2 to 5 (Flebogamma© 5%, 1 g adjusted weight per day) and methylprednisolone from day 6 to 11 (1 g adjusted weight per day), no clinical response with either of the two treatments. No prophylactic anticoagulation was administered.

During her stay at the intensive care unit the patient developed an irreversible intracranial hypertension syndrome with uncal and subfalcial herniation with a poor outcome. Limitation of therapeutic effort was decided and immunoglobulin and corticosteroid treatments were discontinued on the second day. Palliative sedation was started and patient finally died on day 21 after the event.

Discussion

We describe the case of a patient with a fatal intracerebral haemorrhage that developed a moderate

thrombocytopenia with the presence of anti-PF4 antibodies 16 days after the first dose of ChAdOx1-S vaccine (Oxford-AstraZeneca). Intracerebral haemorrhage after vaccination as a rare complication of TTS has been reported before [6].

Thrombosis with thrombocytopenia is a syndrome whose aetiology is thought to be immune-mediated and it is based on the combined presence of a thrombosis and new onset thrombocytopenia within 30 after initial vaccination with ChAdOx1-S vaccine. A confirmed syndrome requires no alternative explanation for the condition (i.e., no heparin exposure within the previous 100 days) [1].

Vaccination against SARS-CoV-2 virus has emerged as a rapid and effective prevention strategy in the face of the current pandemic. On February 2021 several cases of unusual thrombotic events and thrombocytopenia were observed after vaccination with AstraZeneca's COVID-19 vaccine. Thromboses reported were cerebral venous sinus thrombosis or involvement of other unusual territories, such as venous thrombosis in splanchnic territory or arterial thrombosis [4,5]. As a result, on March 15th, vaccination with AstraZeneca's vaccine was detained by some European countries due to safety concerns. In Spain, after April 7th, the vaccination was limited for people under 60 years [7]. All published reports of cerebral venous sinus thrombosis following ChAdOx1-S vaccination showed severe thrombocytopenia due to a mechanism similar to that observed in autoimmune heparin-induced thrombocytopenia [8]. Blood tests at diagnoses usually showed low platelets counts and high D-dimers values. Most of patients had high titters of anti-platelet factor 4 (PF4)-heparin antibodies that strongly activates platelets in vitro without heparin. The presence of anti-PF4-heparin antibodies detected by immunoassays, in the absence of heparin therapy, is highly specific for TTS.

An immune mechanism has been suggested in TTS. This adverse effect could be related to adenovirus vector-based DNA vaccines as it has not been associated with other vaccines against SARS-CoV-2 yet. It has been proposed that as part of an inflammatory and immune reaction the vaccination might induce the formation of autoantibodies against PF4. In the phase I-II clinical trials that led to the approval of the ChAdOx1-S vaccine, no thrombotic events were detected [2]. The estimated incidence of TTS is around 1 case per 100,000 vaccinees under the age of 60 [8].

World Health Organization recent advises for TTS treatments includes avoid the use of heparin and platelet infusion for individuals with TTS following vaccination with a COVID-19 vaccine. WHO recommends the use of Intravenous Immunoglobulin and non-heparin-based anticoagulants (fondaparinux, argatroban or direct oral anti-Xa inhibitors) for individuals with TTS anticoagulation (if no contraindicated) should be started with. Plasmapheresis should be considered if thrombocytopenia is resistant to these measures [1,9].

Immune thrombocytopenia is a known cause of intracerebral cerebral haemorrhage specially when platelet count is below 50×10^9 L. It has been proposed as the etiology of the cerebral spontaneous bleeding [10]. In this case we ruled out other primary and secondary etiologies of intracerebral haemorrhage. The patient showed moderate thrombocytopenia and a TTS was confirmed with the presence of anti-PF4 antibodies. These results suggest that thrombocytopenia was the most probable cause of brain bleeding in our patient.

In conclusion, we present a case of cerebral haemorrhage after an immunological reaction of the ChAdOx1-S vaccine confirmed by laboratory tests. Some cases of intracranial haemorrhage in the setting of TTS have been reported so far. This case highlights an important but fortunately rare complication of TTS which represents an adverse effect of ChAdOx1-S vaccine. Although the most common clinical manifestations of TTS are thrombosis, haemorrhagic events can also appear, probably due to thrombocytopenia, and special treatment considerations must be taken into account.

Further studies are needed to elucidate the mechanisms underlying this thrombotic and haemorrhagic events after ChAdOx1-S vaccine and to assess better preventive and treatment strategies for the clinical management of TTS.

References

1. World Health Organization. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (STT) following vaccination to prevent coronavirus disease. URL: https://apps.who.int/iris/bitstream/handle/10665/342999/WHO-2019-nCoV-STT-2021.1-eng.pdf. Date of consultation: 16.07.2021.
2. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020; 396: 467-8. Erratum in: Lancet 2020; 396:466. Erratum in: Lancet 2020; 396: 1884.
3. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet 2021; 397: 881-91. Erratum in: Lancet 2021; 397: 880.

4. Cines DB, Bussel JB. SARS-CoV-2 Vaccine-induced immune thrombotic thrombocytopenia. N Engl J Med 2021; 384: 2254-6. Erratum in: N Engl J Med 2021; 384: e92.
5. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med 2021; 384: 2092-101.
6. Bjørnstad-Tuveng TH, Rudjord A, Anker P. Fatal cerebral haemorrhage after COVID-19 vaccine. Tidsskr Nor Laegeforen 2021; 141. English, Norwegian.
7. AEMPS. Vaxzevria (vacuna frente a la COVID-19 de AstraZeneca): actualización sobre el riesgo de trombosis (safety note). URL: https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/seguridad-1/2021-seguridad-1/vaxzevria-vacuna-frente-a-la-covid-19-de-astrazeneca-actualizacion-sobre-el-riesgo-de-trombosis. Date of consultation: 16.07.2021.
8. Hernández AF, Calina D, Poulas K, Docea AO, Tsatsakis AM. Safety of COVID-19 vaccines administered in the EU: should we be concerned? Toxicol Rep 2021; 8: 871-9.
9. Dougherty JA, Yarsley RL. Intravenous immune globulin (IVIG) for treatment of autoimmune heparin-induced thrombocytopenia: a systematic review. Ann Pharmacother 2021; 55: 198-215.
10. Neunert C, Noroozi N, Norman G, Buchanan GR, Goy J, Nazi I, et al. Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review. J Thromb Haemost 2015; 13: 457-64. doi: 10.1111/jth.12813.

Hemorragia intracerebral fatal asociada al síndrome de trombosis con trombocitopenia tras la vacuna ChAdOx1-S

Introducción. La pandemia por COVID-19 ha tenido un impacto devastador en la salud, la sociedad y la economía en el mundo. Por ello, las vacunas contra el coronavirus del síndrome respiratorio agudo grave 2 (SARS-CoV-2) han surgido como medida importante para combatir la pandemia. ChAdOx1-S (Oxford-AstraZeneca) es una vacuna vectorizada por adenovirus que expresa la proteína de espiga del SARS-CoV-2. Se han notificado varios casos de trombosis y trombocitopenia inusuales tras la ChAdOx1-S que imitan la trombocitopenia autoinmune inducida por heparina. Esta situación se denomina síndrome de trombosis con trombocitopenia (STT), y se han descrito casos de hemorragia intracerebral secundaria.

Caso clínico. Presentamos un caso de hemorragia intracerebral tras la vacunación con ChAdOx1-S. Una paciente de mediana edad sin antecedentes médicos de interés fue atendida en urgencias 16 días después de la primera dosis de ChAdOx1-S con una hemiplejía izquierda de inicio repentino y una cefalea opresiva holocraneal grave. No recibió heparina los 100 días anteriores. El análisis de sangre mostró trombocitopenia moderada y en la tomografía computarizada se observó una hemorragia lobar frontal derecha sin trombosis en la venografía por tomografía computarizada. Se confirmó la presencia de anticuerpos contra el factor 4 de las plaquetas en la sangre. La paciente presentó un síndrome de hipertensión intracraneal resistente al tratamiento y falleció tres semanas después.

Conclusiones. El STT es un efecto adverso infrecuente de la vacuna ChAdOx1-S que se define por la presencia de trombosis en localizaciones infrecuentes. En nuestro caso, describimos una hemorragia intracerebral espontánea secundaria a la trombocitopenia desencadenada por el STT. Representa una presentación clínica poco frecuente del STT.

Palabras clave. Accidente cerebrovascular. Hemorragia intracerebral. Síndrome de trombosis con trombocitopenia (STT). Trombocitopenia autoinmune. Vacuna ChAdOx1-S. Vacuna COVID-19.