



SCIENTIFIC LETTER

Venous sinus thrombosis following vaccination with ChAdOx1 nCov-19[☆]



Trombosis de senos venosos tras vacunación con ChAdOx1 nCov-19

Dear Editor:

Cerebral venous sinus thrombosis (CVST) is a rare entity that often attacks young people (under 50) and represents 0.5%–1% of all strokes reported.¹ The coronavirus 2019 (COVID-19) pandemic has had a tremendous impact on society and the healthcare system. To this date, the development of vaccines is the main therapeutic tool available.² We describe 2 cases of CVST that required admission to the intensive care unit (ICU).

Case #1 is a 30-year-old man who was admitted to the ER with intense headache of 8-day evolution after receiving the first dose of the vaccine of the recombinant adenoviral vector that codifies the antigen of the spike protein of the acute respiratory distress syndrome (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). There were no findings on the cranial computed tomography (CT) scan performed. After 8 h at the ER, the patient still complained of a headache showing elevated D-dimer levels that went from 5360 ng/mL to 49 732 ng/mL. The cranial CT scan with vascular study was repeated (venogram included) and revealed the presence of a superior longitudinal CVST (Fig. 1A and B). Patient's disease progressed into thrombocytopenia (78 000 platelets/ μ L), and eventually the diagnosis of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) was confirmed testing positive for anti-platelet factor 4 (anti-PF4) antibodies using the enzyme-linked immunosorbent assay (ELISA) technique. The patient developed generalized tonic-clonic seizures with low level of consciousness and a Glasgow coma scale (GCS) of 6 (M: 4, O: 1, V: 1). He was admitted to the ICU with presence of dilated non-reactive pupils. A different cranial CT scan was performed that confirmed the presence of a left parietal acute venous infarction with signs of hemorrhagic transformation and significant cerebral swelling. Together with the Neurosurgery and Neuroradiology Unit, it was decided to implant an external ventricular drainage (EVD) catheter followed by mechanical thrombec-

tomy. Procedures were performed uneventfully and proper angiographic results after 2 passes with the Retriever[®] stent (Stryker Neurovascular, Kalamazoo, MI, United States) were confirmed on the digital subtraction angiography. The patient developed refractory intracranial hypertension to third level measures. The transcranial Doppler echocardiography revealed the presence of systolic waves. The patient remained on argatroban in doses of 0.5 μ g/kg/min to 1 μ g/kg/min adjusted for an activated partial thromboplastin time of 1.5 to 3 times with respect to control, and non-specific human immunoglobulins (Flebogamma[®]; Grifols, S. A., Barcelona, Spain) at doses of 1 g/kg/day for 3 days. Finally, on day 4, the diagnosis of brain dead was confirmed.

Case #2 is a 64-year-old woman admitted to the ER due to headache of 2-week evolution with worsening 48 h prior to admission and walking instability. She had just received the first dose of the ChAdOx1 nCov-19 vaccine. The patient had a good level of consciousness (GCS 15). The cranial CT scan confirmed the presence of a right cerebellar infarction with hemorrhagic transformation while the vascular study revealed the presence of CVST to the right transverse sinus (Fig. 1C and D). The patient had thrombocytopenia (64 240 platelets/ μ L) and elevated D-dimer levels of up to 51 292 ng/mL. She was then transferred to our center where a possible VIPIT study was conducted that would be later confirmed with positivity for anti-PF4 antibodies. The patient was managed conservatively and kept on neuro-monitoring. Anticoagulant therapy with argatroban and Flebogamma[®] was administered at similar doses compared to case #1. Twelve hours after ICU admission, the patient started showing non-reactive mydriasis in her right pupil and a lowered level of consciousness with an impaired GCS of 8 (M: 4, O: 2, V: 2). The cranial CT scan revealed the presence of hydrocephaly. It was decided to implant an EVD catheter. Disease progression was favorable, and the patient was weaned from mechanical ventilation on day 5 and the EVD catheter removed on day 10. After ICU discharge (day 11), the patient remained conscious, collaborative without neurological focality and a modified Ranking scale score of 1. A summary of the patient's analysis and clinical characteristics is shown on Table 1.

CVST is a rare entity with an annual incidence rate between 0.22 and 1.57 for every 100 000 inhabitants. It mostly affects young women (35 to 40 years) and is associated with genetic or acquired thrombotic states.¹

It has been confirmed that SARS-CoV-2 infection is a risk factor for developing CVST. A retrospective study showed a higher rate of CVST after the beginning of the COVID-19 pandemic (42.8 per million of inhabitants), which is higher compared to patients with influenza (RR, 3.83, 95%CI, 1.56-

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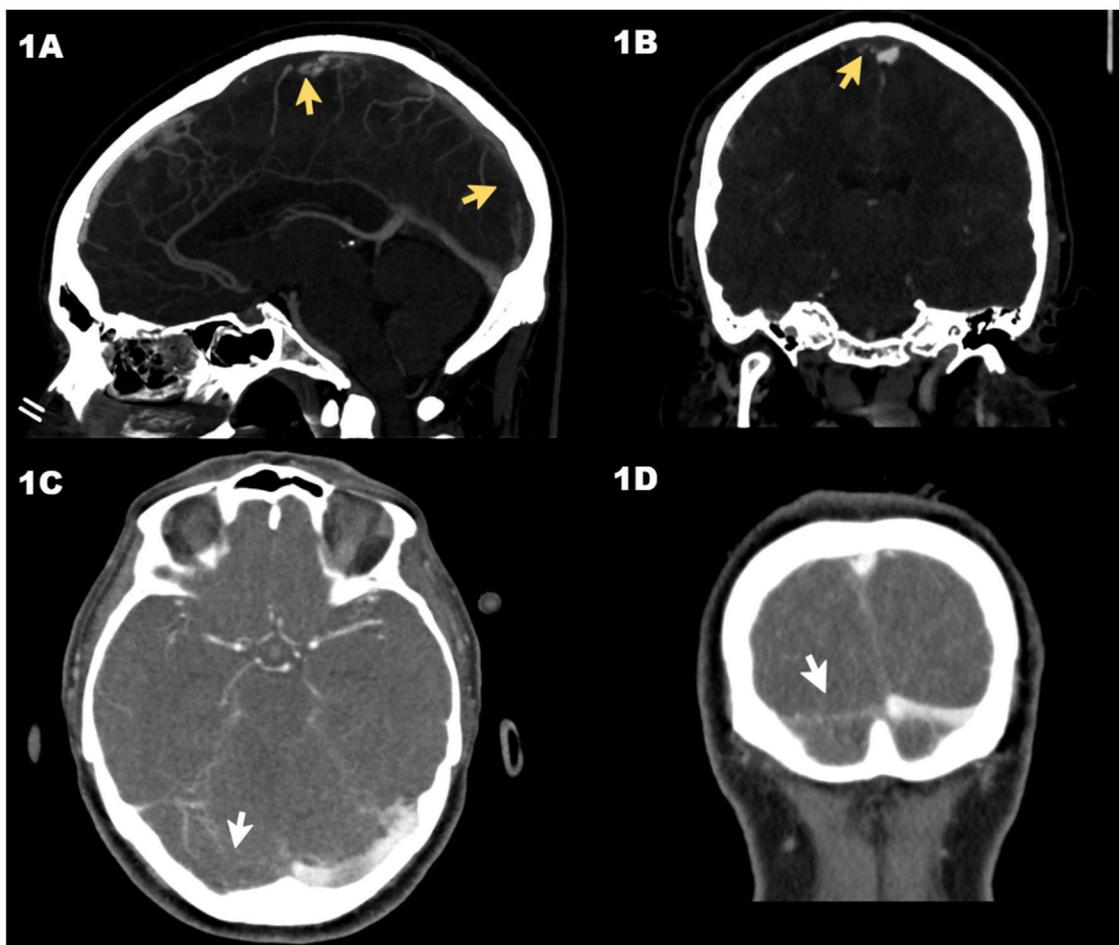


Figure 1 Axial computed tomography (CT) scan in venous phase (case #1) showing the thrombosis of the superior longitudinal venous sinus (arrows) in sagittal (A) and coronal (B) views. CT scan in venous phase (case #2) showing the lack of repletion of the right transverse venous sinus (arrows) in the sagittal (C) and coronal (D) views.

9.41, $P < .001$), and people who received the mRNA vaccine (RR, 6.67, 95%CI, 1.98-22.43, $P < .001$).³

Recently, episodes of thrombosis and thrombocytopenia have been associated with the use of certain vaccines against SARS-CoV-2 (the so-called VIPIT). Seemingly, its etiopathogenesis is due to an autoimmune mechanism similar to the one reported in heparin-induced thrombocytopenia.⁴ Its management and diagnosis are not fully understood. However, a high mortality rate, the appearance of thrombosis in unusual sites, and the presence of anti-PF4 antibodies have been reported in heparin-naïve patients.^{4,5}

After the appearance of the first few cases of CVST in Spain, the use of the ChAdOx1 nCov-19 vaccine⁶ was suspended in this country. By the time the second hospitalization was reported, Spain had already administered 3,817,930 doses of the ChAdOx1 nCov-19 vaccine, out of which 161 800 had already been administered in our region (Castile-La Mancha).⁷ According to the 5th report on pharmacovigilance published by the Spanish Agency of Medicines and Medical (AEMPS), 11 cases of VIPIT had already been reported in Spain, 3 of which resulted in death.⁸ We reported on 2 cases of TSVC associated with the ChAdOx1 nCov-19 vaccine, 1 of which resulted in death. The management

of this entity followed the international recommendations with immunoglobulins and anticoagulant therapy with argatroban. We should mention that fondaparinux, bivalirudin, and direct factor Xa inhibitors like rivaroxaban and apixaban are feasible alternatives to argatroban.⁹

The heterogeneity reported in the clinical presentation complicates its early approach, which can have an impact on results.⁵ The patient who died had longer times since he was admitted to the ER until diagnosis was achieved (18 h 42 min vs 1 h 32 min), until ICU admission (25 h 18 min vs 6 h 09 min), and until target anticoagulation was reached (33 h 20 min vs 22 h 29 min). Mechanical thrombectomy was not useful either despite the good angiographic result reported.

To this date, CVST is an extremely rare entity whose association with the vaccine has been cause for alarm due to its severity and the impact that suspending the administration of the vaccine would have under the present circumstances. However, many aspects still need to be elucidated regarding origin, presentation, disease progression, prognosis, and management. We should mention here that a normal CT scan does not exclude the diagnosis of CVST. In any case, accelerating the diagnostic and therapeutic approach can impact the results, which is why it is important to pay attention

Table 1 Summary of the clinical and analytical characteristics, treatments, and results of the 2 cases reported.

Characteristics	Case #1	Case #2		
Age (years)	30	64		
Sex	Male	Female		
Past medical history	None	Hyperactive bladder, osteoporosis		
Previous treatment	None	Tramadol plus paracetamol, solifenacin, denosumab		
Vaccine-hospitalization time (days)	8	22		
ER-diagnosis time (h)	18 h 42 min	1 h 32 min		
ER-ICU time (h)	25 h 18 min	06 h 09 min		
ER-target anticoagulation time (h)	33 h 20 min	22 h 29 min		
Symptoms	Sudden headache, myalgias	Headache, nausea, vomiting, walking instability		
Location of the lesions	Thrombosis of superior longitudinal sinus, left parietal infarction with hemorrhagic transformation, cerebral edema	Thrombosis of right transverse venous sinus, cerebellar infarction with hemorrhagic transformation		
GCS (M, O, V) during ICU assessment	GCS 6 (M: 4, O: 1, V: 1)	GCS 15 (M: 6, O: 4, V: 5)		
Pupil alterations	Dilated and non-reactive (bilateral)	Non-reactive unilateral mydriasis (right pupil)		
Seizures	Yes	No		
Anti-PF4 antibodies	Positive	Positive		
Anticoagulation	Argatroban	Argatroban		
Other therapies	Immunoglobulins, EVD catheter, mechanical thrombectomy	Immunoglobulins, EVD catheter		
Results at ICU discharge	Dead		Alive	
	Admission	Nadir (day)	Admission	Nadir (day)
Platelets (100–400 × 1000/μL)	212	9 (3)	64	49 (2)
APTT (20–38.0 s)	25	90.2 (3)	30	65.7 (3)
TT (15.8 s)	17	NA	19.2	NA
Prothrombin activity (70% to 120%)	88	18 (3)	87	35 (3)
INR (0,8–12)	1.1	3.8 (3)	1,07	1.9 (3)
Fibrinogen (derived, 180 mg/dL to 350 mg/dL)	492	272 (2)	229	234 (2)
D-dimer (0.0 ng/mL to 500.0 ng/mL)	5360	220 914 (2)	51 292	64 805 (2)
CRP (0–8.0 mg/dL)	26.7	100.7 (2)	47.9	50.2 (2)
SARS-CoV-2 CRP	Negative		Negative	

APTT, activated partial thromboplastin time; CRP, C-reactive protein; EVD, external ventricular drainage; GCS, Glasgow Coma Scale; h, hours; ICU, intensive care unit; INR, international normalized ratio; M, motor; mg/dL, milligrams per deciliters; NA, not assessed; ng/mL, nanograms per deciliters; O, ocular; PF4, platelet factor 4; s, seconds; SARS-CoV-2 RCP, polymerase chain reaction of severe acute respiratory distress syndrome coronavirus 2; TT, thrombin time; U/L, units per liter; V, verbal.

to patients who, after vaccinated, present with compatible clinical signs.

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Hemodynamic monitoring for liver transplantation: Agreement between invasive and non-invasive devices?



Monitorización hemodinámica para trasplante de hígado: ¿concordancia entre dispositivos invasivos y no invasivos?

Dear Editor,

Liver transplantation (LT) is characterized by bleeding, circulatory volume fluctuations, vascular clamping/unclamping and major fluid shifts, resulting in significant circulatory instability.¹ A meta-analysis conducted by Cecconi et al. concluded that hemodynamic monitoring strategies coupled with therapy decisions, reduces mortality in high-risk surgical patients.² Invasive thermodilution has long been the gold standard in estimating cardiac output (CO).³ As an easy-to-use noninvasive device, NICOM[®] uses thoracic bioactance to analyze the variations in voltage in each cardiac contraction in response to high-frequency current. Previous studies have shown mixed results regarding the performance of bioactance for measuring CO in various populations.⁴⁻⁶ We aimed to evaluate whether bioactance can be used as an alternative CO monitoring technique in liver transplantation.

We performed a prospective non-randomized study from September to November 2019 and recruited all patients admitted for elective LT. Re-transplants or emergency LT were excluded. All patients had a Pulse Contour Cardiac Output (PiCCO[®]) device placed in the femoral artery and

a central venous catheter placed in the internal jugular vein according to the established transplant's protocol. After LT surgery, patients were sequentially included for placing a Cheetah Medical NICOM[®] device. Cardiac index (CI) was recorded at admission and every 8 h during the first 48 h. CI recorded from PiCCO[®] was measured three times using the transpulmonary thermodilution technique and after injecting 20 mL boluses of cold normal saline via a central venous catheter. System was calibrated before each group of measurements and performed by the same person. If the variation among readings was higher than 10%, one additional measurement was taken for an average reading. Data was expressed as mean values and standard deviation (SD). The difference in CO between the two techniques was calculated as the mean \pm 1.96 \times SD which were called 95% limits of agreement; the percentage error was calculated using the formula $(100 \times 1.96 \times$ SD of bias between the two methods)/mean between the two methods. Mean percentage error was considered acceptable if $<30\%$. Correlations were tested using the Pearson correlation coefficient. Agreement between thermodilution/bioreactance was tested using Bland–Altman analysis and intraclass correlation coefficient (ICC).⁵⁻⁷ Conclusions obtained from bioactance did not influence medical decisions. Institution Ethics Committee approved the study.

Twenty-nine patients were recruited but only 20 fulfilled the inclusion criteria. A total of 420 paired observations were collected as described in Table 1. After LT, as a result of fluid resuscitation, cumulative fluid balance increased as well as ELWI measurements. There was good agreement between thermodilution-CI and bioactance-CI (3.44 ± 0.87