

Ischaemic stroke as a presenting feature of ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia

Talal Al-Mayhani¹, Sadia Saber¹, Matthew Stubbs², Nick Losseff¹, Richard J Perry^{1,3}, Robert J Simister^{1,3}, David Gull⁴, Hans Rolf Jäger^{3,5}, Marie Scully², David J Werring^{1,3}

¹Comprehensive Stroke Service
National Hospital for Neurology and Neurosurgery
University College Hospitals NHS Foundation Trust
Queen Square
London WC1N 3BG, United Kingdom

²Department of Haematology
University College Hospitals NHS Foundation Trust
London NW1 2PG, United Kingdom

³Stroke Research Centre
UCL Queen Square Institute of Neurology
First Floor
Russell Square House
10-12 Russell Square
London WC1B 5EH, United Kingdom

⁴Department of Stroke Medicine
Sandwell General Hospital
Sandwell and Birmingham Hospitals NHS Trust
Birmingham
Sandwell General Hospital
West Bromwich, West Midlands, B71 4HJ, United Kingdom

⁵Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation,
UCL Queen Square Institute of Neurology,
National Hospital for Neurology and Neurosurgery
Queen Square
London WC1N 3BG, United Kingdom

Corresponding author:

Professor David J Werring

Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square
Institute of Neurology, Russell Square House, 10 - 12 Russell Square, London WC1B 5EH, UK.

Tel: +44 (0)20 3108 7493

Fax: +44 (0)20 7833 8613

Email: d.werring@ucl.ac.uk

Word count: 537 (body text, without references)

A syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) has recently been reported following the ChAdOx1-nCoV-19 (Oxford–AstraZeneca) recombinant adenoviral vector vaccine encoding the spike glycoprotein of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).¹⁻⁴ Previously described patients developed thrombosis, mainly affecting cerebral venous sinuses, with thrombocytopenia and antibodies to platelet factor 4 (PF4), but the characteristics of VITT with arterial thrombosis have not previously been described. Here, we report three patients with VITT who presented with ischaemic stroke.

Patient 1, a 35-year-old Asian female, developed episodic right temporal and periorbital headache 6 days after receiving the ChAdOx1-nCoV-19 vaccine. Five days later she awoke with left face, arm and leg weakness, right gaze preference and drowsiness. Non-contrast CT and CT angiography revealed occlusion of the right middle cerebral artery distal M1 segment with extensive ischaemia and haemorrhagic transformation (Figure 1A-C). Subsequent imaging revealed right portal vein thrombosis. The platelet count was 64,000 per cubic millimetre (reference range 150,000 to 400,000), D-dimer was raised at 11,220 µg/L (reference range 0 to 550) and the Asserachrom HPIA IgG assay for anti-PF4 antibodies was positive (76.1%). The patient underwent urgent decompressive hemicraniectomy (Figure 1D). The platelet count increased after intravenous immune globulin and plasmapheresis. She received anticoagulation with intermediate dose fondaparinux. Fourteen days after presentation her conscious level suddenly dropped; CT head showed extensive haemorrhagic transformation of the left middle cerebral artery infarct with mass effect and herniation of the brain through the decompressive hemicraniectomy. Brainstem death was subsequently confirmed.

Patient 2, a 37-year-old White female, presented 12 days after receiving the ChAdOx1-nCoV-19 vaccine with diffuse headache, left visual field loss, confusion, and left arm weakness. CT angiography showed occlusion of both internal carotid arteries (Figure 1E) and left transverse sinus thrombosis (Figure 1F); diffusion-weighted MRI showed bilateral acute infarcts in a borderzone distribution (Figure 1G,H). Subsequent imaging confirmed pulmonary embolism, and thromboses of the left transverse and sigmoid sinuses, left jugular, right hepatic and both iliac veins. The platelet count was 9,000 per cubic millimetre, D-dimer was raised at 34,000 µg/L, and the anti-PF4 antibody assay was positive (99.7%). The platelet count increased following treatment with intravenous immune globulin, two intravenous pulses of methylprednisolone and plasmapheresis; the patient then received fondaparinux and improved clinically.

Patient 3, a 43-year-old Asian male, presented 21 days after the ChAdOx1-nCoV-19 vaccine with dysphasia. CT and MR showed an acute left frontal and insular infarct corresponding to the anterior cortical territory of the left middle cerebral artery, with a small volume of haemorrhagic transformation within the infarct. MR and CT venography showed no evidence of cerebral venous sinus thrombosis. The platelet count was 48,000 per cubic millimetre, D-dimer was raised at 24,000 µg/L and the anti-PF4 antibody assay was positive. He was treated with platelet transfusion, intravenous immune globulin and fondaparinux and remains stable.

Our observations suggest that, in addition to venous thrombosis, the neurological spectrum of VITT can include arterial occlusion. Young patients presenting with ischaemic stroke after receiving the ChAdOx1-nCoV-19 vaccine should urgently be evaluated for VITT with laboratory tests (including platelet count, D-dimers, fibrinogen and anti-PF4 antibodies), and

managed by a multidisciplinary team (haematology, neurology, stroke, neurosurgery, neuroradiology) for rapid access to treatments including intravenous immune globulin, methylprednisolone, plasmapheresis and anticoagulation with fondaparinux.^{1,3,5}

Figure Legend:

Patient 1 (A-D): Non-enhanced CT (A) shows hyperdense clot in distal right M1 segment (arrow), which corresponds to site of the occlusion demonstrated on the CT angiogram (B, arrow). The non-enhanced CT at the level of the basal ganglia (C) shows a large acute right MCA infarct with loss of grey-white matter differentiation (arrows) and early haemorrhagic transformation (short arrow). A non-enhanced CT following emergency craniectomy (D) demonstrates swelling of the right hemisphere and extension of the haemorrhagic transformation (short arrows)

Patient 2 (E-H): the extracranial CT angiogram (E) shows occlusion of both internal carotid arteries (arrows); the right being occluded from its post-bulbous portion, and the left at its origin. The intracranial CTA (F) demonstrates patent middle cerebral arteries bilaterally (arrows), which fill via collaterals predominantly from the posterior communicating arteries. There is also lack of filling of the mid- and distal portions of the left transverse sinus (short arrow), suspicious of a thrombosis, later confirmed with a dedicated CT venogram. MR diffusion weighted images (G and H) reveal several acute infarcts in the right occipital lobe (arrow in G) and centrum semiovale bilaterally (arrows in H), corresponding to cortical as well as deep and superficial arterial borderzone territories.

Contributorship

DJW and MSc had the idea for the paper. T A-M prepared the first draft with DJW and SS. HRJ prepared the draft figures. MSt, NAL, RJP, RJS and DG were involved in the clinical care of the patients. All authors critically reviewed the manuscript for intellectual content.

References

1. Scully M, Singh D, Lown R, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. *The New England Journal of Medicine* 2021. DOI: 10.1056/NEJMoa2105385.
2. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *The New England Journal of Medicine* 2021. DOI: 10.1056/NEJMoa2104840.
3. Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *The New England Journal of Medicine* 2021. DOI: 10.1056/NEJMoa2104882.
4. Cines DB, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. *The New England Journal of Medicine* 2021. DOI: 10.1056/NEJMe2106315.
5. Oldenburg J, Klamroth R, Langer F, et al. Diagnosis and Management of Vaccine-Related Thrombosis following AstraZeneca COVID-19 Vaccination: Guidance Statement from the GTH. *Hamostaseologie* 2021. DOI: 10.1055/a-1469-7481.