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Letter to the Editor

Multiple internal border zone infarcts in a patient with COVID-19 and CADASIL

A R T I C L E   I N F O

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Dear Editor,

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the commonest inherited stroke disorder. We report a novel presentation of multiple internal border zone infarcts in a patient with COVID-19 and CADASIL. The clinical significance of this case is to highlight the risk of COVID-19 exacerbating CADASIL. Possible pathophysiological mechanisms are discussed, which may be extrapolated to patients with cerebral small vessel disease and non-CADASIL strokes.

1. Case report

A 38-year-old woman presented with sudden onset of a mild dysarthria (NIHSS 1), with a prodrome seven days earlier of fever, myalgia, anosmia and ageusia. Her past medical history was unremarkable. There was a family history of CADASIL, genetically confirmed in her father and sister. A CT brain showed low attenuation within the right corona radiata; CT angiogram of the head and neck vessels was unremarkable. She was commenced on aspirin 300 mg and admitted. Nasopharyngeal swab confirmed infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). An MRI brain demonstrated chronic small vessel disease consistent with a pattern seen in CADASIL and acute infarcts in eleven locations bilaterally within an internal border zone distribution. (Fig. 1. A-C) Her observations on day eight from onset of COVID-19 symptoms saw a spontaneous blood pressure drop from 119/66 mmHg to 89/47 mmHg, with an associated deterioration of her dysarthria and a transient right facial droop. On day eleven she had a sudden deterioration with severe unintelligible dysarthria, mild oro-pharyngeal dysphagia, right hemiparesis and facial weakness with increased tone and past pointing in the left upper limb (NIHSS 9). An MRI brain on day thirteen demonstrated one new acute infarct in the same territory with a confluence of some lesions as they had increased in size. (Fig. 1. D-F) IgM for anticardiolipin antibodies was elevated at 14 U/ml (0 – 10), whilst all other investigations were within normal parameters. Genetic analysis of the NOTCH3 gene demonstrated a heterozygous pathogenic missense variant c.268C > T (p.Arg90Cys). On discharge she had moderate to severe dysarthria and a mild facial droop whilst all other neurological symptoms had improved (Modified Rankin Score 2), with neurorehabilitation planned in the community.

2. Discussion

CADASIL is an inherited angiopathy caused by pathogenic mutations in the NOTCH3 gene on chromosome 19, characterised by aberrant protein formation, the presence of granular osmiophilic deposits within endothelial cells and endotheliitis by accumulation of inflammatory cells and apoptosis, but not to date in the cerebrovasculature [5]. SARS-CoV-2 gains entry into the host via the angiotensin-converting enzyme 2 (ACE2) receptor, which is present in all arterial endothelial and smooth muscle cells, and therefore subsequent endothelial dysfunction could trigger a thrombotic cascade. Indirect

Abbreviations: DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; T2, transverse relaxation time; FLAIR, Fluid-attenuated inversion recovery

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endothelial dysfunction with secondary thrombosis could be due to a combination or single systemic factors which would include: inflammatory cytokine production, activation of a coagulation cascade, and complement mediated microvascular thrombosis; as evidenced by elevated inflammatory markers and D-dimer levels [2,4,6]. Additionally, antiphospholipid antibody production have been described with COVID-19, however, such antibodies can be seen in many acute infections transiently without conferring an increased risk of thrombosis [2]. Hypoxia may also trigger endothelial dysfunction but was not documented in this case.

A second mechanism proposed is hypoperfusion due to cerebral blood flow dysautoregulation, secondary to disruption of the renin-angiotensin system (RAS) by COVID-19. Given the location of the arteriopathy in the small vessels of patients with CADASIL this would make the internal border zone particularly vulnerable to hypoperfusion.

There is evidence of chronic cerebral hypoperfusion in CADASIL, with a proposed mechanism being impairment in the myogenic component of autoregulation where vascular smooth muscle constricts or dilates to transmural pressure changes [1]. Internal border zone infarcts have been reported in nine patients with CADASIL; whereby six had documented systemic hypotension, one occurring with intercurrent Influenza A infection [7]. In this case, only a minor transient hypotension was documented with associated clinical deterioration. Broadening this mechanism of injury to non-CADASIL strokes, bilateral frontotemporal hypoperfusion has been described in patients with severe COVID-19 [8]. We propose the mechanism of injury is related to the RAS; which has separate regulatory pathways in both the periphery and the brain. This can be disrupted by SARS-CoV-2 due to the down regulation of ACE2 receptors, causing limitations on vasodilatation [9].

Additional mechanisms may involve endothelial dysfunction in

Fig. 1. MRI brain performed on day 7 from onset of COVID-19. (A, B) DWI demonstrating high-intensity lesions with low ADC values consistent with acute infarcts in eleven locations bilaterally (all not shown) within an internal border zone distribution between the lenticulostriate perforators and the deep penetrating cortical branches of the middle cerebral artery in the corona radiata and centrum semiovale, and at the deep white matter branches of the anterior and the middle cerebral artery. (C) FLAIR hyperintensity in multiple foci, including the deep white matter, periventricular and subcortical regions. Repeat MRI performed on day 13 from onset of COVID-19. (D, E) DWI and (F) FLAIR sequences demonstrating one new lesion and a confluence of some lesions as they had increased in size.
CADASIL as a predisposing factor with limited reserve when challenged with such an insult as COVID-19 [1]; or a superimposed secondary parainfectious autoimmune disorder for which there is growing radiological and histological evidence [10].

The clinical significance of this case is to highlight for the first time the association of COVID-19 and CADASIL, and given the risk of exacerbation we would advise patients to abide by strict infection prevention measures for the duration of the pandemic. A wider implication of this report is to highlight proposed pathophysiological mechanisms of stroke in the context of CADASIL and COVID-19, which may inform the mechanism of non-CADASIL strokes. We propose that the primary mechanism of infarcts is endothelial injury causing a secondary microvascular thrombosis and also hypoperfusion due to cerebral blood flow dysautoregulation due to impairment of the RAS. We recommend that further research be conducted into the pathophysiology of COVID-19 related stroke and therapies that target stabilising the vascular endothelium.

Declarations of Competing Interests
None.

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Owain Hedd Williamsa,⁎, Saamir Mohideena, Arup Senb, Olivera Martinovic,Jonathan Hartc, Peter Anthony Brexa, Laszlo Krisztian Sztrihaa

a Department of Neurology, King’s College Hospital, London, UK
b Department of Stroke Medicine, Princess Royal University Hospital, London, UK
c Department of Neuroradiology, King’s College Hospital, London, UK

E-mail address: owain.williams2@nhs.net (O.H. Williams).