

## **Raised intracranial pressure (pseudotumour cerebri) associated with SARS-CoV-2**

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Word count: 1,458 words

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Several neurological sequelae of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are now described.<sup>1</sup> We describe a pair of cases demonstrating a novel association between Covid-19 and severely raised intracranial pressure (ICP). Patient 2 is included as part of a summary of 43 cases of Covid-19 neurology.<sup>1</sup>

A 29 year old female nurse of Indian origin with a body mass index (BMI) of 25 and a background of hypothyroidism developed intermittent, low intensity headaches, particularly affecting the left hemicranium, six weeks after onset of SARS-CoV-2 respiratory illness. These headaches became bifrontal after a week and were associated with intermittent blurring of distance vision and pulsatile tinnitus. She then developed neck pain and sudden onset chest pain radiating across the anterior chest wall, into the back and down both arms with nausea and vomiting. Investigations showed a normal electrocardiogram (ECG), Troponin T and blood tests, except for a microcytic anemia; computerised tomography (CT) of the head was normal. She was discharged home. Two days later she had a significant deterioration in her vision and was no longer able to use her mobile telephone or see faces clearly. She presented to hospital two days later and was admitted with ongoing severe chest and back pain, which was exacerbated in an upright posture and alleviated by lying flat. Her neurological examination revealed significantly reduced visual acuities (right eye 6/36 and left eye 1/60) and she was unable to read the Ishihara test plate for colour vision in either eye. She had Frisén Grade V papilledema bilaterally (Fig. 1A-D) and severely reduced visual fields, predominantly affecting the nasal hemifields bilaterally (Fig. 2A and B). Blood tests revealed a microcytic anemia with hemoglobin 99 g/L (115 – 155 g/L), mean corpuscular volume 76 fL (80 – 99 fL). There was an iron deficiency with iron level 3 µmol/L

(6 – 35  $\mu\text{mol/L}$ ), transferrin saturations 4% (20 – 45%) and ferritin 8  $\mu\text{g/L}$  (13 – 150  $\mu\text{g/L}$ ).

Erythrocyte sedimentation rate (ESR) was elevated at 77 mm/hr (1 – 20 mm/hr). SARS-CoV-2 serology was positive (Roche Immunoassay). Lupus anticoagulant was positive with negative cardiolipin and beta-2 glycoprotein antibodies. She had an elevated D-dimer 940  $\mu\text{g/L}$  (0 – 550  $\mu\text{g/L}$ ) and elevated fibrinogen 4.5 g/L (1.5 – 4 g/L) and normal coagulation protocol. Total protein was elevated at 84 g/L (60 – 80 g/L), Immunoglobulin G (IgG) and Immunoglobulin A (IgA) were normal with elevated Immunoglobulin M (IgM) 4.2 g/L (0.4 – 2.3 g/L). Other results including a vasculitis and microbiology screen were normal.

The day after admission she had magnetic resonance imaging (MRI) of the head with contrast which demonstrated typical features of raised ICP with dilated optic nerve sheaths. Contrast opacification within the dural venous sinuses was normal. The next day she had a lumbar puncture which demonstrated a cerebrospinal fluid (CSF) opening pressure of >80 cmCSF, with normal constituents; with CSF drainage the pressures were reduced down to 40 cmCSF. Due to further deterioration in her vision the next day to perception of light only, she had a further lumbar puncture, which demonstrated a CSF opening pressure of >110 cmCSF, and the pressures were reduced down to 20 cmCSF. She was transferred as an emergency that evening to a regional neurosciences centre and a lumbar drain was inserted the following day. The radicular thoracic pain improved immediately after the lumbar drain. She had a catheter venogram which demonstrated bilateral transverse/sigmoid sinus stenoses, with significant pressure drops of >20 mmHg at each. She was started on acetazolamide at 250mg twice daily. Venous stenting was considered, but after discussion the transverse/sigmoid sinus stenoses were thought to be secondary to the raised ICP. Nine days after the lumbar drain was inserted the CSF pressures remained elevated whenever the lumbar drain was clamped, and therefore a lumboperitoneal shunt was inserted. By

eleven days after the shunt insertion, visual acuities had improved to 6/12 in her right eye and to 6/60 in her left eye. Colour vision was normal (13/13 Ishihara), with improving papilledema appearances and visual fields. Two months after discharge from hospital her vision had improved, with visual acuities in the right eye of 6/9 (corrected with 6/6 with pinhole) and left eye of 6/36. Her visual fields had also improved, with only mild loss of sensitivity persisting in the nasal fields of both eyes (Fig. 2C and D). The papilledema resolved (Fig. 1E and F) but Optical Coherence Tomography (OCT) scanning now showed thinning of the peripapillary retinal nerve fibre layer temporal to both optic discs as well as some secondary subfoveal scarring (Fig. 1G and H). Repeat blood tests revealed the ESR had reduced to 40 mm/hr (1 – 20 mm/hr). Lupus anticoagulant remained positive with negative cardiolipin and beta-2 glycoprotein antibodies. IgM was elevated at 3.25 g/L (0.4 – 2.3 g/L).

A 16 year old female patient of Sri Lankan origin with a normal BMI on the 81<sup>st</sup> centile (normal BMI range 3<sup>rd</sup> – 90<sup>th</sup> centile) presented with a five day history of fever, back pain, vomiting, then headaches and a sore throat, suggestive of SARS-CoV-2 respiratory illness. The headache had no other significant features. She had a C-reactive protein (CRP) of 294 mg/L (0 – 5 mg/L) and pyrexia, an elevated troponin T of 1979 ng/L (0 – 14 ng/L) and an elevated D-dimer of 855 µg/L (0 – 550 µg/L). A chest radiograph demonstrated bibasal infiltrates. Clinically this was consistent with a probable Covid-19 illness, as determined using World Health Organisation criteria [‘Global surveillance for human infection with coronavirus disease (Covid-19)’]. Four naso-pharyngeal swabs for SARS-CoV-2 were negative. She did not have clinical serology testing performed as it was not clinically available at the time. However, she was recruited to a fluid biomarker study<sup>1</sup> of patients with clinically probable Covid-19 infection and CNS presentations, in which ~85% of

individuals had positive SARS Cov-2 IgG in contemporaneous samples (the study ethics only permit group level reporting). Her ECGs showed T wave inversion in V1-V3. An echocardiogram demonstrated a small pericardial effusion and she was diagnosed with myopericarditis and commenced on colchicine. Blood tests, including a vasculitis and microbiology screen were normal.

Nine days after the onset of her Covid-19 symptoms she reported horizontal diplopia particularly looking to the right. By this point she was systemically well and the CRP had improved. She had right sided headaches, worse on lying down and in the mornings, without significant photophobia or phonophobia. She had a right abducens palsy without papilledema (Fig. 2E-G). Two days later the abduction failure had worsened. There was a partial left sided lower motor neuron facial nerve palsy. Two days further on she had developed a left abducens palsy and increased left orbicularis oculi weakness.

An MRI head two days after the onset of diplopia was normal but a repeat MRI head with venography 10 days later demonstrated signs consistent with raised ICP with no evidence of a venous sinus thrombosis.

A lumbar puncture 5 days after the onset of the diplopia demonstrated an elevated CSF opening pressure of 39 cmCSF, with normal CSF constituents. A repeat lumbar puncture 5 days later showed an opening pressure of 27 cmCSF. Acetazolamide was commenced the next day at 250mg twice daily. The headaches, diplopia and left facial nerve palsy improved over the subsequent few days, with full resolution by follow up review at eight weeks.

### **Discussion:**

The proposed mechanisms of raised ICP in idiopathic intracranial hypertension include venous sinus stasis, reduced CSF drainage across arachnoid granulations, increased venous

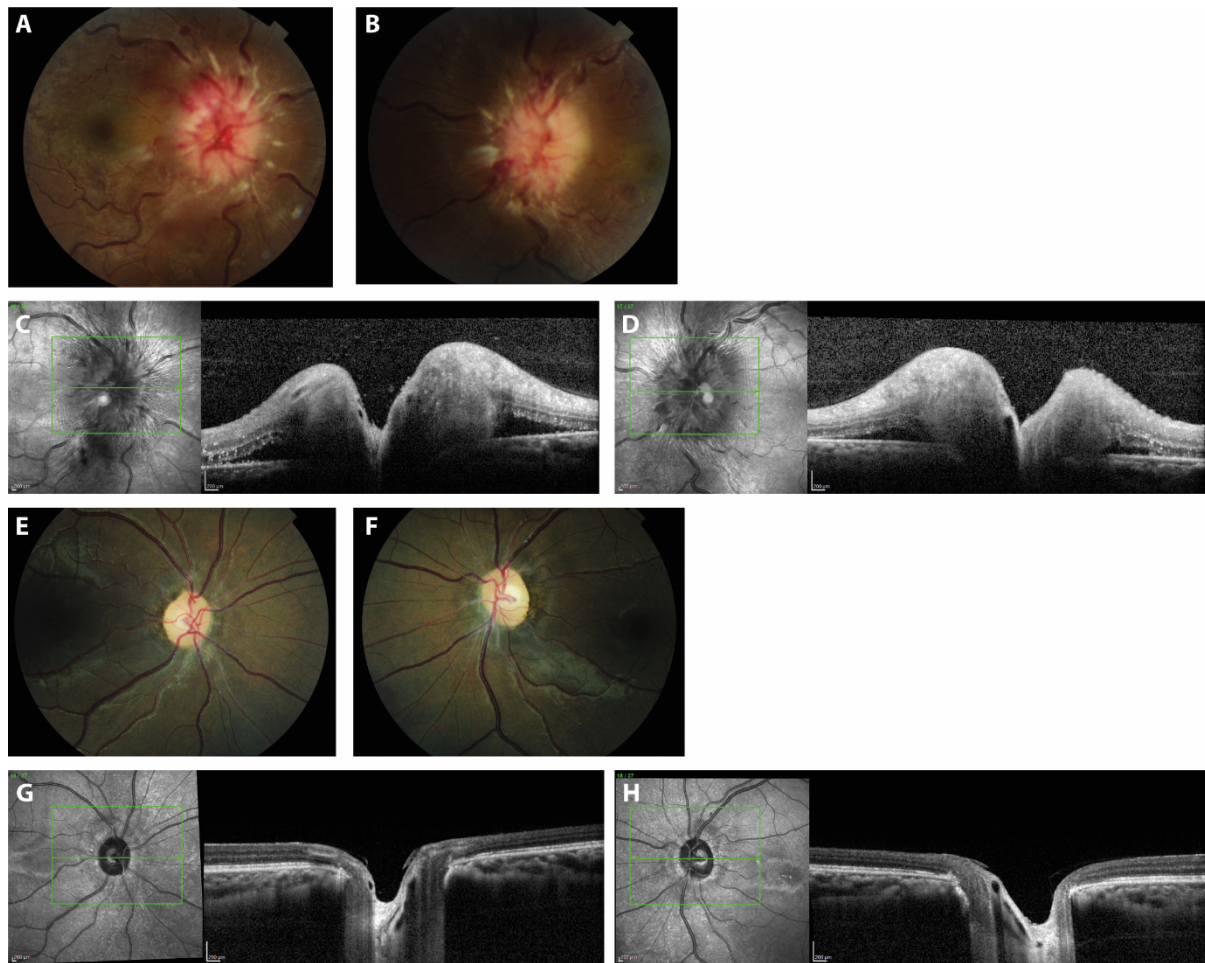
sinus pressure from venous sinus stenosis and congestion of the glymphatic system, with contribution of inflammatory and thrombophilic factors.<sup>2,3</sup> Covid-19 is associated with a pro-thrombotic coagulopathy and hyperviscosity,<sup>4</sup> with microvascular and macrovascular thromboses.<sup>5</sup> The second case had some features seen in children with multi-system inflammation with gastrointestinal and cardiac involvement, supporting an inflammatory mechanism in part.<sup>6</sup> In this case series, we hypothesise that SARS-CoV-2 infection led to a pro-inflammatory and pro-thrombotic state evident on blood biomarkers, resulting in venous stasis, impaired glymphatic flow, raised ICP, and consequently, venous sinus stenoses. The first case also had a slightly high BMI and an iron deficiency anemia which could have been contributory factors.<sup>7</sup> Her most severe symptom initially was thoracic and chest pain, reflecting radicular pain which has been described in raised ICP.<sup>8</sup> The second case developed abducens palsies secondary to the raised ICP, and a left facial nerve palsy also likely due to the raised ICP, which has been reported previously.<sup>9</sup> In the context of the Covid-19 pandemic there is a theoretical risk of infection transmission to clinicians when performing ophthalmoscopy.<sup>10</sup> In light of the risk of missing raised ICP, and the potentially significant consequences illustrated by these cases, we advocate for fundoscopy to be undertaken early and safely in patients presenting with headache and visual symptoms during the current Covid-19 pandemic.

## **Acknowledgements**

RB is funded by a National Institute of Health Research (NIHR) Academic Clinical Lectureship in Neurology. OS is supported by the UCLH NIHR Biomedical Research Centre. The serology study was supported by a grant from the UCLH NIHR Biomedical Research Centre.

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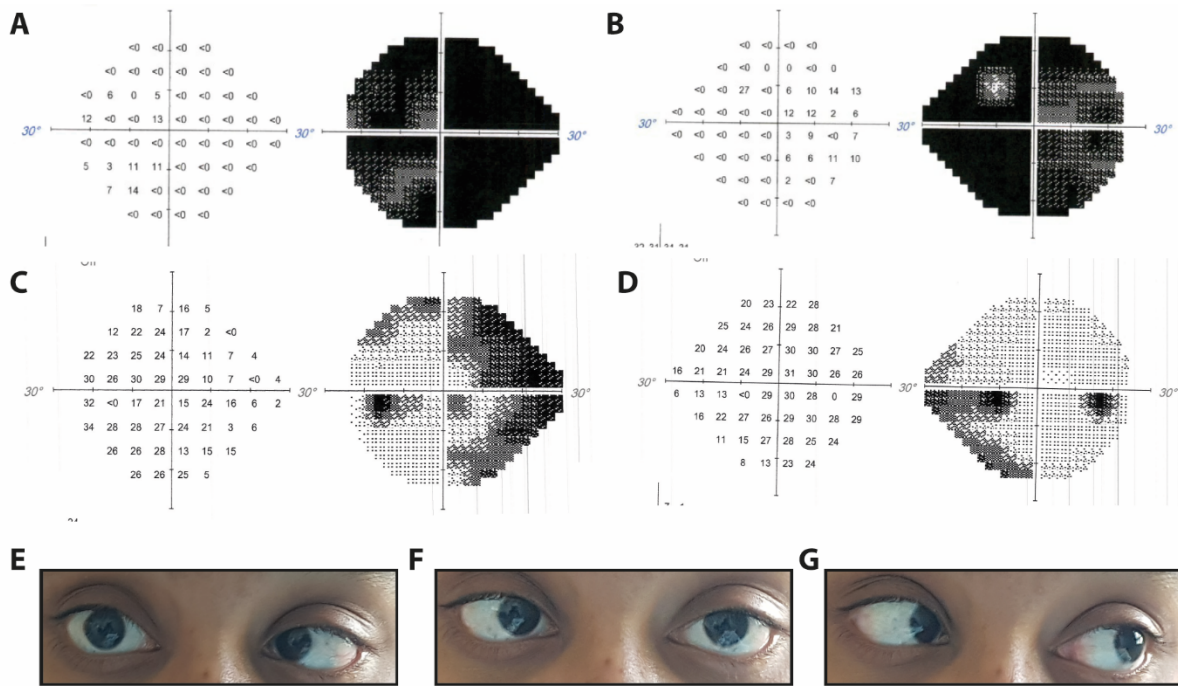
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**Figure 1 Ophthalmological assessments of Case 1**

**Case 1 A and B** Retinal photographs demonstrate marked bilateral papilledema (Frisén grade 5) affecting the left eye (B) more than the right (A) with prepapillary and peripapillary haemorrhages and cotton wool spots. **C and D** Spectralis Optical Coherence Tomography (OCT) images of the right (C) and left (D) optic discs showing subretinal and intraretinal fluid tracking from the disc. **E and F** Follow up retinal photographs reveal that the papilledema has resolved in both the right (E) and left eye (F). **G and H** Follow up OCT images of the right (G) and left (H) optic discs showed thinning of the peripapillary retinal nerve fibre layer temporal to both optic discs, as well as some secondary subfoveal scarring.





**Figure 2 Visual field assessments of Case 1 and Eye movements of Case 2**

**A and B** 24-2 Swedish Interactive Testing Algorithm (SITA) Fast visual field testing was performed. Humphrey Visual fields of the left (A) and right (B) eyes demonstrate severely reduced visual fields, predominantly affecting the nasal hemifields bilaterally. **C and D** Humphrey Visual fields of the left (C) and right (D) eyes repeated two months after discharge from hospital demonstrate improved visual fields, with only mild loss of sensitivity persisting in the nasal fields of both eyes. **Case 2** External photographs of the Case 2 patient's right gaze (E), primary position (F), and left gaze (G). These demonstrate an esotropia in primary gaze, which worsens in right gaze, and there is an abduction deficit of the right eye. These findings are consistent with an abducens palsy on the right.