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Severe cortical damage associated with COVID-19 case report

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ABSTRACT

Symptoms of COVID-19, as reported during the SARS-CoV-2 pandemic in 2019-2020, are primarily respiratory and gastrointestinal, with sparse reports on neurological manifestations. We describe the case of a 17-year old female with Cornelia de Lange syndrome and well controlled epilepsy, who sustained significant cortical injury during a COVID-19 associated multi-inflammatory syndrome.

1. Introduction

During the pandemic of SARS-CoV-2, which began in late 2019, reported symptoms of; COVID-19 are primarily associated with respiratory or gastrointestinal issues. However, there is increasing evidence of neurological manifestations; as per Ellul et al., 7% of hospitalised patients in Wuhan, China and 69% of intensive care patients in France were reported to have encephalopathy. Several case reports describe new onset seizures in COVID-19, especially in severe forms of the infection (1). However, the majority report brief, self-limiting seizures in children, the impact of which seems to have been limited; in contrast we report the case of a 17-year-old female who sustained significant cortical injury during the course of COVID-19 associated multi-inflammatory syndrome.

2. Case

This case describes a 17-year-old female with Cornelia de Lange syndrome and well controlled epilepsy with infrequent brief tonic-clonic seizures; who at neurological baseline was able to mobilise by shuffling her body from a seated position and to indicate her needs non-verbally.

She presented with cough, fever and difficulty in breathing. Due to

an increasing oxygen requirement she was initially started on high flow oxygen but continued to require FiO₂ 80 % to maintain SaO₂ above 94 %. In view of her work of breathing and oxygen requirement a decision was made to intubate and transfer to the paediatric critical care unit. She showed signs of sepsis (spiking fevers, HR 120–130bpm, BP systolic 120 mmHg, capillary refill time <2 s). Her bloods showed CRP 275 mg/L, ferritin 2091 microgram/liter, deranged clotting (PT 13.4 s, INR 1.3, APTT 38 s, fibrinogen 3.75 g/L) and bone marrow failure (Hb 73 g/L, plt $51 \times 10^9/L$, WCC $2.7 \times 10^9/L$). A chest x-ray showed bilateral hilar consolidation.

Respiratory secretions were positive for SARS-CoV-2, Influenza-b and *Pseudomonas aeruginosa*. Her hospital stay was complicated by acute kidney injury (urea 5.4 mmol/L, creatinine 93umol/L), ventricular tachycardia, rhabdomyolysis (CK rose to 7822 unit/L, LDH 570 mmol/L) and severe exposure keratitis of both eyes. Her condition improved, despite persistent fevers. On day 20 she was extubated and noted to be more responsive.

Two days later she had a sudden respiratory deterioration requiring re-intubation. Her chest x-ray showed complete white out of the left lung and her inflammatory markers increased significantly from CRP 127 to CRP 345 mg/liter fulfilling criteria for Paediatric Multi-Inflammatory Syndrome temporally related to COVID (PIMS-TS). Repeat bacterial

Abbreviations: COVID-19, disease caused by SARS-CoV-2; SaO₂, arterial oxygen saturation; FiO₂, fractional inhaled oxygen; HR, heart rate; BP, blood pressure; CRP, C-reactive protein; Hb, haemoglobine; plt, platelets; WCC, white cell count; PIMS-TS, paediatric multiinflammatory syndrome temporally associated with COVID-19.

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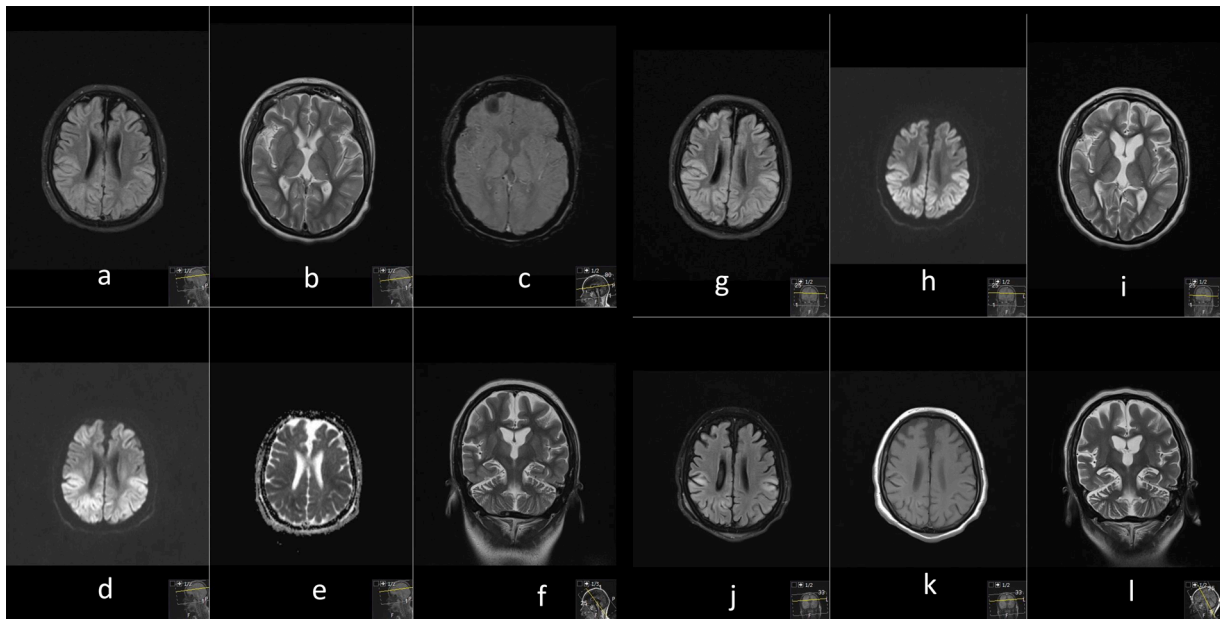


Fig. 1. Serial contrast enhanced MRI brain performed prior to illness and at 3 time points during current illness.

Previous MRI f: supra- and infra-tentorial neuroparenchymal volume loss (arrows).

Initial MRI

(a, d, e,) multifocal areas cortical swelling in both cerebral hemispheres.

(b) abnormal signal change in the thalami (arrow).

(d,e) mild restricted diffusion.

(c) There were no microhaemorrhages on SWI sequence.

Repeat MRI performed 7 days later. FLAIR and DWI sequences (g-h) demonstrated similar areas of cortical signal change and signal change in the thalami (i). Normal appearances of the spinal cord (images not shown).

Follow up MRI performed 23 days later. k: reduced signal change in the cortices and thalami with volume loss and high T1 signal in some of the affected cortices suggestive of laminar necrosis (arrow).

There is increased widening of the sulci and enlargement of ventricles indicating interval parenchymal volume loss (l).

and viral screen was negative. On day 25 she developed an episode of tachycardia with mouth clenching and pupillary dilatation. EEG was performed and showed Bi-PLED: ongoing subclinical ictal activity. In view of this, levetiracetam was increased and the episodes did not recur. Continual EEG monitoring was not available on our unit, but amplitude-integrated 2-channel EEG did not show any signs of seizure activity. On day 27 she had further episodes of tachycardia and tachypnoea that settled with benzodiazepines and phenytoin.

MRI brain performed on day 30 showed widespread bilateral cortical, cerebellar and thalamic signal change and swelling. Repeat EEG on day 31 showed diffuse cerebral dysfunction with no ongoing seizure activity so treatment was continued.

Further episodes of suspected seizures persisted over the following week requiring midazolam infusion and phenobarbitone. They settled on day 35 after Clobazam was started. Lumbar puncture showed raised protein of 908 mg/L but no pleocytosis and tested negative for bacterial culture and viral PCR. Repeat MRI on day 37 showed persistent multifocal areas of neuroparenchymal signal change but no new areas of injury. Of note she had a third increase in inflammatory markers beginning on day 46, which was treated with pulse methylprednisolone. Follow-up MRI 53 days into her illness showed evolving laminar necrosis in the areas previously affected (Fig. 1B).

As of 7 months into her illness, she is now tracheostomy-ventilated and undergoing long-term neurorehabilitation. She is able to respond consistently to environmental cues but remains well below her prior functional level.

3. Discussion

Cornelia de Lange syndrome is a genetic condition that in this case

presented with growth and developmental delay, limb deformities, head and face signs, hirsutism and epilepsy. Her neurodisability was likely a contributing factor to the severity of her presentation with COVID-19, though her respiratory function had previously been normal.

Coronaviruses have been associated with neurological disease for several decades and theories of virus-induced neuropathology caused by misdirected host immune response have been postulated for several years. One study into the neurological manifestations of COVID-19 found CNS symptoms in 25 % of patients [1] but seizures were reported in only 0.5 %.

Of those with neurologic manifestations specific MRI brain findings have been reported to be linked to COVID-19. An observational case series from France reported neurologic features in 84 % (49/58) adult inpatients with acute respiratory distress syndrome (ARDS) due to COVID-19. MRI of the brain was performed in 13 patients of which 8 patients had enhancement in leptomeningeal spaces and 3 had ischaemic stroke [2]. A retrospective study from Turkey showed 21 % (50/235) ICU patients developed neurological symptoms of which 54 % (27/50) had brain MRI 44 % (12/27) of which was abnormal. COVID-19 related neuroimaging findings were reported in 10/27 (37 %) cases as cortical FLAIR signal abnormality with prominent white matter changes [3].

To our knowledge, this is the first case report showing this pattern of evolving cortical brain damage in association with late-onset seizures and PIMS-TS. These seizures were distinct to the patient's usual epileptic seizures and we hypothesise that the severe systemic inflammation played a key role in exacerbating both her epilepsy and the resulting brain injury as the pattern of injury was not typical of that seen in uncontrolled status epilepticus with widespread cortical, thalamic and posterior fossa involvement [4] with only limited evidence of

supra-refractory status epilepticus. However, we recognize that a continuous EEG monitoring might have revealed non-convulsive status epilepticus for a longer period of time than clinically apparent. Early recognition and treatment of seizures in children with COVID-19 and PIMS-TS may be important to minimise damage and optimise outcomes.

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None to declare

Declaration of Competing Interest

The authors declare no conflicts of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.seizure.2020.11.014>.

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