# Corpus callosum in COVID-19 cytokinopathy, an update

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**Case Report**

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# Abstract

The corpus callosum (CC) connects frontal, parietal, occipital and temporal cortices in the brain. We report a disconnection syndrome as a manifestation of coronavirus disease 2019 (COVID-19) encephalopathy. Like prior coronaviridae, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects the brain over a spectrum of injury. Present communication is the first description of white matter involvement confined to CC's commissural fibers in their entirety. Until case registries, longitudinal studies and animal models clarify any direct neurotropism of SARS-CoV-2; this case is consistent with recent biological evidence suggesting a cytokine mediated excitotoxic injury concomitant with the severity of infection.


# Introduction

The corpus callosum (CC), with commissural fibers connecting frontal, parietal, occipital and temporal cortices, is the largest white matter bundle in the brain. Its clinical *disconnection* syndromes [1, 2] represent a disruption of bi-hemispheric continuity. [3] CC's anterior half (genu, rostrum, body) contains fibers interconnecting frontal association areas; the isthmus contains mostly primary motor, somatosensory and auditory fibers; and in the splenium, primary visual, association temporooccipital and parietal commissural fibers are aligned with the hippocampal commissure. The isthmus and the posterior splenium are dense with large diameter axons, whereas the genu and anterior splenium are invested by small fiber axons. Beyond an understanding of CC's normal anatomical and physiological state, neuroimaging efforts continue to assign signatures typical for discrete pathological mechanisms of congenital, inflammatory, tumoral, degenerative, infectious, and even vascular nature. [4]

Coronavirus (CoV) is an enveloped positive-sense, single-stranded RNA virus. Human pathogenic Coronaviridae include HCoV-229E, HCoV-OC43, HCoVHKU1, HCoV-NL63, severe acute respiratory syndrome CoV (SARS-CoV), Middle East respiratory syndrome CoV (MERS-CoV) and now severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19). We report a patient with COVID-19 related encephalopathy in a pandemic where the profiling of hypoxic and ischemic sequelae has overshadowed other potential mechanisms of CNS injury. Similar to neurological manifestations among prior coronavirus contagions, [5] reports of COVID-19 indicate diverse forms of brain injury. [6, 7] The present communication is the first description of an isolated but, diffuse involvement of CC's commissural fibers. As such, it supports a cytokine mediated excitotoxic injury to CNS, associated with COVID-19 infection. [4, 8]

# Case

The patient is a 26-year-old right-handed high school educated African American female. Beginning the third week of April, she started to complain of headache, runny nose, and cough. Her other medical morbidities included uncontrolled type 1 diabetes mellitus (on insulin), obesity, chronic kidney disease stage III (diabetic nephropathy), recurrent yeast (monilial) vaginitis, and a serum test positive for herpes

simplex type 2 in 2019. Her developmental history was significant for a left brachial plexus injury (Erb's palsy) from a prolonged labor and a genu varum which were treated with orthoses and corrective surgery, respectively.

She was positive for SARS - COV 2 via nasopharyngeal swab PCR after being exposed to her mother who was subsequently hospitalized in an intensive care unit (ICU). Patient herself presented to emergency room with fever, diffuse headache, exertional dyspnea, myalgia, fatigue, nausea, abdominal pain, diarrhea, and loss of appetite soon after. There was no associated chest pain, palpitations, photophobia, phonophobia, weakness, dizziness, or other sensorimotor symptoms.

First examination revealed an awake, conversational, and oriented obese female with no focal neurological findings but, relative tachypnea, tachycardia, hypertension, and a temperature of 39.2 C. She was saturating 98% on pulse oximetry at room air. Pertinent laboratory values [reference range] included a serum glucose of 212 mg/dl [70 mg/dl – 99 mg/dl], creatinine of 2.7 mg/dl [0.6 mg/dl – 1.0 mg/dl], blood urea nitrogen of 34 mg/dl [7 mg/dl – 19 mg/dl], magnesium 1.6 mg/dl [1.6 mg/dl – 2.6 mg/dl] and lipase 771 IU/L [8 IU/L – 78 IU/L]. Patient also had an elevated C-reactive protein at 66.9 mg/L [0 mg/dl – 5 mg/dl], normocytic anemia of 7.9 gm/dl [12 gm/dl – 16 gm/dl], ferritin 1784 ng/ml [5 ng/ml – 204 ng/ml], fibrinogen of 651 mg/dl [191 mg/dl – 491 mg/dl] and a peak D-dimer of 10,180 ng/ml [270 ng/ml – 490 ng/ml]. Blood and urine cultures were negative for an infection.

Chest x-ray was hypo-inflated with mild bibasilar airspace opacities. She was administered intravenous fluids and placed on isolation precautions. Overnight she became hypoxic and lethargic requiring supplemental oxygen. Care was escalated to a stepdown level, in view of worsening kidney injury, metabolic acidosis and alteration of consciousness. The patient was alert but, speech was now limited to "*yes, no* and *hurts*" responses. Cranial nerves were intact, strength was symmetric and sensory modalities were preserved. A non-contrast CT (NCCT) head was negative for acute pathology.

A stroke alert was later initiated for an acute onset of focal sensory deficits when she could not feel pain on her left arm during phlebotomy. On this assessment she was essentially without speech, responding only with nods of her head but, able to follow simple motor instructions. Cranial nerve and motor exam were normal except for her Erb's palsy but, her sensation to light touch was diminished on the left arm and leg. NCCT head on this occasion revealed a hypodense corpus collosum along its entire length. (Fig. 2A)

The next morning, she remained alert and oriented to being in a hospital. Speech was mildly dysarthric. Comprehension was intact but, she could not name, repeat or write. Cranial nerves, strength and sensation were preserved. Toes were down and no gross ataxia was present on movements of limbs on her right. Her left arm was apractic. The development of a disconnection syndrome with putative etiologies being either vascular, inflammatory, or infectious was entertained. An acute hypoxic respiratory failure requiring intubation, with non-oliguric acute kidney injury, normocytic anemia, and encephalopathy delayed further neurologic investigation. She received tocilizumab, steroids, remdesivir and convalescent

plasma exchange as treatment modalities for a severe COVID-19 infection. A dysexecutive syndrome was noted once the acute medical issues began to resolve. [9]

4 weeks from onset, her exam became referable to the dominant parietal lobe. Now extubated, she was making a steady recovery from her COVID-19 infection and had recently tested negative. While no longer aphasic or agraphic, she scored 19/30 on Montreal Cognitive Assessment (MoCA), for impairments in visuospatial/executive tasking, and calculation. (Fig. 1) She had a hoarse voice from a vocal cord palsy, without other cranial nerve anomalies. There was no new weakness. Her sensation was preserved to all exteroceptive and interoceptive modalities symmetrically across gross dermatomes. She continued to exhibit an apraxia of her left upper extremity. Finally, she had developed a finger agnosia of the left hand with suggestions of left-right disorientation.

A contrast enhanced MRI brain 18 days after the initial CT scan confirmed an expansile T2 hyperintense signal along the complete length of corpus callosum associated with restriction of diffusion, and T1 prolongation. (Fig. 2B and C) There was no superimposed susceptibility or pathologic enhancement. While a CT angiogram was not feasible with her kidney injury, no large vessel occlusions were identifiable from gradient echo (GRE), turbo spin echo (TSE), susceptibility weighted imaging (SWI) and post contrast MR sequences.

A diagnosis of probable COVID-19 encephalitis manifesting as a disconnection syndrome [1] was made. Additional attempts to consolidate a cytokine mediated excitotoxic injury through the burden of interleukins in cerebrospinal fluid (CSF) [5] and exclusion of a direct viral or auto-immune mediated encephalitis were abandoned in view of the clinical propriety of discharge after a prolonged stay in the hospital.

She continued to recuperate in brain injury rehabilitation for dyspraxia of left upper extremity, speech, swallowing, ambulatory dysfunction, and neuropsychiatric derangements (left visuospatial neglect, insomnia, mood and adjustment disorders). [9] An MRI brain repeated since discharge demonstrated an improving encephalitis by virtue of normalizing ADC values.

# Discussion

It is likely that COVID-19 will be associated with diverse injuries of the nervous system. [7] The present case demonstrates clinical and radiographic selective involvement of the corpus callosum. Signs of interhemispheric discontinuity: a non-fluent aphasia; unilateral apraxia, and hemi-inattention (alexia and spatial acalculia) on the left; as well as a right-left disorientation are synchronous with a callosal disconnection along its length. Moreover, the diminishing severity of deficits over repeated exams, absence of exposure to any identifiable toxins or offending drugs, expansile character of the lesion, sparing of gray matter and improvement of signal on repeat imaging lend support for an inflammatory mechanism which appeared to vary with the activity of the primary infection. This also has, biological

basis in the distinctive behavior of CC cells in response to cytokines, excitatory amino acids, toxins, and drugs.[4]

Cytokines are polypeptide hormones (~ 10–35 kDa) that regulate tissue homeostasis, through local or external systems. Their expression in normal tissues as biologically active mediators is either quiescent or normal. Cytokines' source, regulation, target, and function in the CNS remain an area of active debate. When stress endangers tissue integrity, cytokines are produced to regulate growth, differentiation, or defense and repair. But when parent systems are overwhelmed, their entry into the circulation and chronic production can have deleterious effects on the nervous system. Among the cytokine family peripheral production of IL-1β and IL-6 can attain levels required to permeate the blood-brain barrier and act on target cells of central origin. Otherwise, cytokine production occurs *on request* in activated microglia, neurons, astroglia, perivascular and endothelial cells. Receptors for interleukins (IL)-l, IL-Z, IL-3, IL-6, TNF-a, and many growth factors, are distributed across the brain according to their function. [10]

Observations from neuronal cultures support small concentrations of cytokines as neurotrophic, whereas higher concentrations are neurotoxic. [11] Cytokines bind glycoprotein receptors on microglia and astroglia to activate intracellular signaling (protein kinase) pathways. [12,13] Activated microglia release reactive oxygen or nitrogen species, directly toxic to oligodendrocytes. They further impair glutamate transporters on astrocytes as well as oligodendrocytes to promote intracellular calcium. [14, 15,16, 17, 18] Such preferential activation of non N-methyl-D-aspartate (NMDA) receptors, astrocytic heterogeneity and higher glutamate transporter activity make white matter such as CC vulnerable to cytotoxic edema.[4, 18, 19] Oligodendrocytes remain susceptible to a cytokine insult when neuronal populations are spared.[4, 14, 16, 19, 20]

Erstwhile analyses from the first CoV contagion demonstrated significant elevation in the expression of CSF cytokine profiles (granulocyte macrophage-colony stimulating factor, IL- 6, IL- 8, and monocyte chemoattractant protein-1) in patients with central nervous system (CNS) involvement. [5] Thus, a cytokine mediated pathophysiology (*cytokinopathy*) needs consideration beyond direct invasion or ischemia. [21, 22]

Alternative mechanisms of injury seem much less likely. Ischemia although described in COVID-19 patients, is not supported in the diffuse involvement of the CC secondary to its diverse vascular supply from multiple tributaries of the carotid and vertebrobasilar systems. [23] Nevertheless, a normal echocardiogram and patent intracranial vessels on brain MRI had negated any association of a stroke. Similarly, hypoxia was exonerated on account of an absolute sparing of areas typically vulnerable to anoxia i.e. hippocampus, neocortex, striatum, and cerebellum. Although, CC lesions frequently lie at the interface of autoimmune demyelinating conditions (multiple sclerosis, neuromyelitis optica spectrum disorder and acute disseminated encephalomyelitis); present lesion was neither asymmetric nor associated with periventricular demyelination. [4] There were no hallmarks in this case to suggest a nutritional deficiency either. [4] Additionally, unlike historical Corona viridae [5] SARS COV2 remains overly elusive in the neural tissue [22] including CSF, reducing support for a direct viral invasion of CNS. [24,25] Sparse reports of CSF positive for nucleocapsid protein genes of COVID 19 await replication.

In summary, a cytokine mediated response to COVID-19 appears to be the most likely mechanism of this patient's injury. Our hypothesis of white matter vulnerability is also consistent with descriptions of olfactory tract involvement and other axonopathies. [6, 7] Cytokine related nervous system injury in response to SARS-CoV-2 will be a fruitful area of future basic research. This also represents an important opportunity for the development of case registries and longitudinal follow ups of COVID-19 patients to investigate causality of this virus across the neuraxis. Careful neurologic evaluations [7] can assist in clarifying these mechanisms and uncover neurotherapeutic targets for immunomodulation.

# Declarations

**Ethics statement:**

Ethics or IRB approval was not applicable to this study. Patient gave written informed consent, in accordance with CARE guidelines and in compliance with the Declaration of Helsinki principles. All authors share responsibility for the conduct, integrity, and reporting of this manuscript.

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# Figures

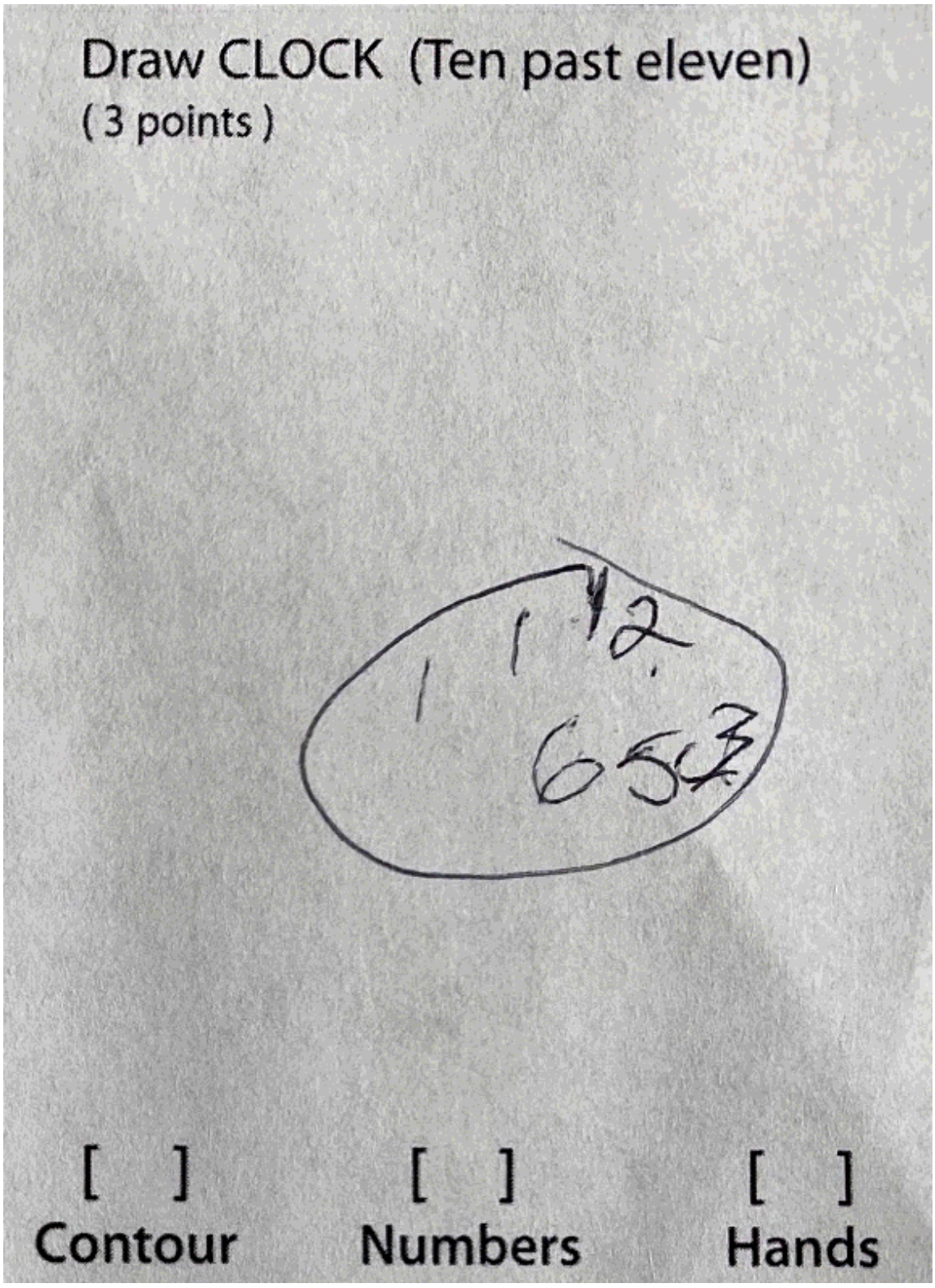
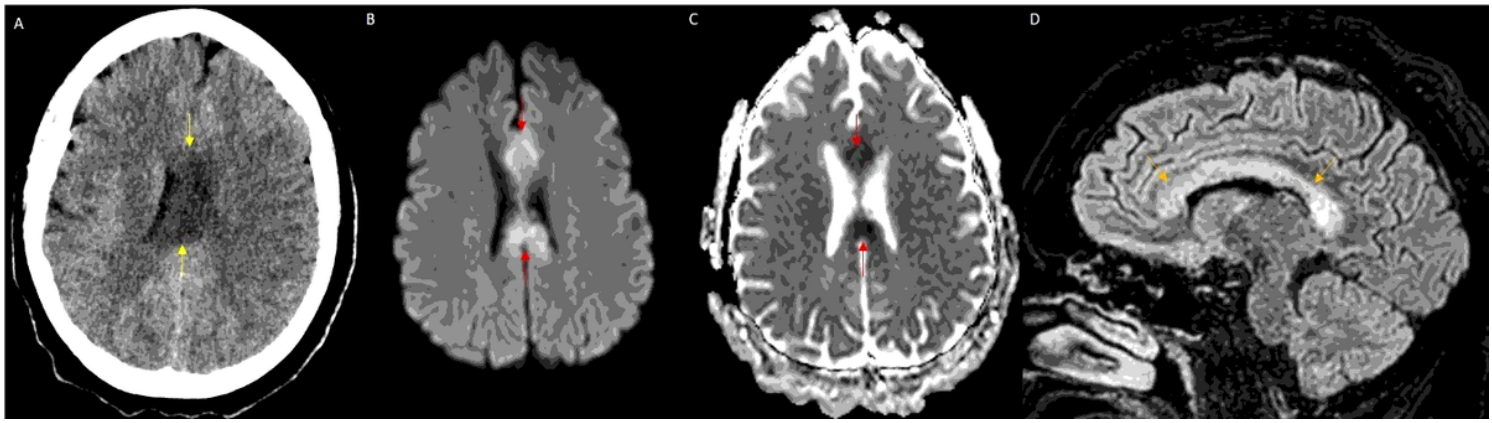



**Figure 1**

Hemi inattention to left visuospatial field on the clock drawing feature of MOCA test. Clinical evidence of degraded visuospatial perception, language processing and motor coordination were the hallmarks of patient's disconnection of the left from right hemisphere. An inability to construct hands (conceptualization) and label numbers specific to the left half of the clock (spatial planning/processing and execution) suggest a lesion in the posterior corpus callosum.




## Figure 2

Diffuse corpus callosum involvement in COVID-19 infection. Axial non contrast CT images (A) obtained on day 5 of admission demonstrate confluent, mildly expansile abnormal hypoattenuation along the entire corpus collosum outlined by yellow arrows. Axial diffusion (B) and ADC (C) images obtained on day 23 of admission demonstrate confluent, mildly expansile increased diffusion signal and decreased ADC signal, consistent with restricted diffusion, along the entire corpus collosum (red arrows). Sagittal 3D T2 fluid attenuated inversion recovery (FLAIR) (D) images from the same study demonstrate corresponding expansile T2 hyperintense signal (orange arrows). Post contrast images (not shown) demonstrated no enhancement or large vessel occlusion.