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Neurological, neuropsychiatric and neurodevelopmental complications of COVID-19

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Abstract

Although COVID-19 is predominantly a respiratory disease, it is known to affect multiple organ systems. In this article, we highlight the impact of SARS-CoV-2 (the coronavirus causing COVID-19) on the central nervous system as there is an urgent need to understand the longitudinal impacts of COVID-19 on brain function, behaviour and cognition. Furthermore, we address the possibility of intergenerational impacts of COVID-19 on the brain, potentially via both maternal and paternal routes. Evidence from preclinical models of earlier coronaviruses has shown direct viral infiltration across the blood–brain barrier and indirect secondary effects due to other organ pathology and inflammation. In the most severely ill patients with pneumonia requiring intensive care, there appears to be additional severe inflammatory response and associated thrombophilia with widespread organ damage, including the brain. Maternal viral (and other) infections during pregnancy can affect the offspring, with greater incidence of neurodevelopmental disorders, such as autism, schizophrenia and epilepsy. Available reports suggest possible vertical transmission of SARS-CoV-2, although longitudinal cohort studies of such offspring are needed. The impact of paternal infection on the offspring and intergenerational effects should also be considered. Research targeted at mechanistic insights into all aspects of pathogenesis, including neurological, neuropsychiatric and haematological systems alongside pulmonary pathology, will be critical in informing future therapeutic approaches. With these future challenges in mind, we highlight the importance of national and international collaborative efforts to gather the required clinical and preclinical data to effectively address the possible long-term sequelae of this global pandemic, particularly with respect to the brain and mental health.

Keywords

SARS-CoV-2, neuroinflammation, vertical transmission, neuropsychiatric complications, anosmia

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Introduction

COVID-19 illness is caused by the coronavirus, SARS-CoV-2, and is proposed to have evolved via mutation of a virus originally reported in horseshoe bats, with pangolins as a putative intermediate species. Although COVID-19 is predominantly a respiratory illness, extrapulmonary manifestations are increasingly recognised, including comorbid neurological, neuropsychiatric, neurodevelopmental and coagulation complications (Gupta et al., 2020). A particular challenge in this regard has been the rapid growth in scientific literature, often in the form of case reports and clinical experiences. Since the range of clinical features have not been well established, such reports are important in identifying new clinical manifestations and therefore pathological mechanisms of action that may lead to novel and effective treatments. However, caution is required interpreting the numerous reports and as such we have not included studies that are yet to undergo peer review.

Epidemiology of the illness

COVID-19 illness typically develops with the onset of fever, dry cough and shortness of breath. Asymptomatic carriers, combined with lack of physical distancing, or social crowding, can contribute to super-spreading events and exponential growth of the contagion. The median incubation period is around 5 days, with 4–5 days between illness onset and medical presentation, and 9 days to hospitalisation (Li et al., 2020a).

Global COVID-19 cases have surpassed 17 million, with close to over 670,000 fatalities (31 July 2020) within the first 7 months of the pandemic. Several factors contribute to this growth including a high reproduction number (R_0), estimated between 2 and 4 but which can be reduced with appropriate measures. 80% of presentations appear to be mild, 15% requiring hospital care (usually for pneumonia) and 5% needing intensive care (Thevarajan et al., 2020). The World Health Organization (WHO) estimated a crude mortality ratio of 3–5% globally, compared with 0.1% for influenza. Case fatality rates (CFRs) are higher in men by 66% and increase dramatically with age (<0.5% under 50, rising to 1.3% in 50s and 14.8% by 80s; Verity et al., 2020). Medical comorbidities including hypertension, diabetes and obesity also increase the risk of multiple organ failure and increase mortality and morbidity. Those with cardiovascular complications have a disproportionately poor outcome, possibly due to the downregulation of 'angiotensin converting enzyme 2' (ACE2) receptors in various systems, leading to cytokine storm and prothrombotic states. The latter may be involved in vascular and thrombotic events beyond the lung, including the central nervous system (CNS).

Clinical reports indicate that, although SARS-COV-2 predominantly affects the respiratory system, it has complex and poorly understood effects on multiple organ systems, including the CNS (Gupta et al., 2020). This includes clusters of neurological symptoms (in 36–84% of cases) such as loss of smell and taste, headaches, fluctuating consciousness and encephalopathy, thrombosis and stroke, particularly in severe illness. Additionally, the Centers for Disease Control and Prevention (CDC) data report more severe outcomes for pregnant COVID-19-positive women compared to non-pregnant women 31.5% vs 5.8% (www.cdc.gov/mmwr/volumes/69/wr/mm6925a1.htm). We review below the evidence from human and animal studies for neurological and neuropsychiatric manifestations of COVID-19 and, while data are limited, we discuss the possible neurodevelopmental impact of COVID-19 in pregnancy and early brain development.

Neurological and neuropsychiatric features of COVID-19

The evidence for CNS involvement in human coronavirus (HCoV) infections is largely derived from case reports of coronavirus family viruses causing Severe Acute Respiratory Syndrome (SARS) and Middle-East Respiratory Syndrome (MERS), both of which have high fatality rates. These studies reported a range of neurological symptoms, including seizures, altered consciousness, focal motor deficits, strokes and encephalitis. They also identified brain scan changes and evidence for viral genetic material in cerebrospinal fluid (CSF) and post-mortem brains (Cheng et al., 2007). In a systematic review of neuropsychiatric complications of severe coronavirus infections (including SARS and MERS), Rogers et al. (2020) noted few psychiatric sequelae of these infections. They identified delirium, agitation and altered consciousness due to COVID-19 and highlighted the need to monitor for psychiatric symptoms post-recovery.

Almost two-thirds of patients with SARS-CoV-2 are reported to manifest loss of smell (anosmia) and/or loss of taste (ageusia) as a presenting symptom (Table 1). These symptoms persist longer than other symptoms. Recognition of such symptoms could aid in rapid identification and case isolation. While evidence from animal studies in other SARS-CoV CNS infections implicated the olfactory pathway as a potential portal to the brain (Wu et al., 2020), another study in SARS-CoV-2 suggested the olfactory epithelium rather than the olfactory nerve is involved (Kerslake et al., 2020). Further studies to assess possible neuroinvasive effects of SARS-CoV-2 are needed, as this may result in direct neurological and neuropsychiatric sequelae affecting the orbitofrontal cortex, hippocampus and amygdala that connect directly with the olfactory nerve.

There are numerous (and rapidly evolving) case series and case reports being published from across the world, predominantly from the Northern Hemisphere where the cases have been high (see Table 1). It is clear that neurological complications occur more

Table 1. Neurological manifestations of SARS-CoV-2 infection (for references see supplementary material).

Authors (year), journal; location of study; date	Study type and description	Key findings
Anosmia and ageusia studies		
Lechien et al. (2020), *Eur Arch of Oto-Rhino-Laryngology*; multi-centre European study; April 6	417 (263 females) mild to moderate COVID-19-positive patients recruited from 12 European hospitals.	85.6% reported olfactory (79.6% of them with anosmia) and 88% gustatory dysfunction. In 11.8%, olfactory dysfunction appeared prior to other symptoms
Eliezer et al. (2020), *JAMA Otolaryngology–Head & Neck Surgery*; France; April 8	Case report of a 40-year-old COVID-19-positive woman with acute loss of smell without nasal obstruction.	MRI showed bilateral inflammatory obstruction of the olfactory clefts but no abnormalities of olfactory bulbs and tracts were noted
Spinato et al. (2020), *JAMA*; Italy; April 22	202 COVID-19 positive mildly symptomatic patients were interviewed by telephone.	Altered sense of smell and taste reported by 64%; more frequent in women; 38% noted it prior to or with other symptoms; and 26% reported after other symptoms
Luers et al. (2020), *Clinical Infectious Diseases*; Germany; May 1	72 COVID-19-positive patients (41 males, mean age = 38 ± 13 years).	Reduced olfaction reported in 74% of patients and diminished sense of taste in 69%. 68% reported both symptoms, while one patient had only reduced taste and four had reduced olfaction only. Both symptoms occurred on average on day 4 after first symptoms (like headache and cough). 13% had reduced smell and taste on day 1 of other symptoms
Other neurological manifestations		
Chen et al. (2020), *BMJ*; Wuhan, China; March 26	113 COVID-19 deaths.	22% presented with disorders of consciousness at admission, vs <1% in those who recovered. 36% noted to have dysexecutive syndrome
Poyiadji et al. (2020), *Images in Radiology*; USA; March 31	Middle-aged female with 3-day history of cough and altered mental status. Tested positive for COVID-19 after initial negative result.	Acute necrotising hemorrhagic encephalopathy with CT showing symmetric hypoattenuation in bilateral thalami. MRI showed hemorrhagic rim-enhancing lesions within the bilateral thalami, medial temporal lobes and subinsular regions
Moriguchi et al. (2020), *International Journal of Infectious Diseases*; Japan; April 3	24-year-old man with a mild respiratory illness presenting with meningism and altered consciousness.	Pleocytosis in CSF, positive CSF SARS-CoV-2 PCR testing, and right mesial temporal lobe abnormalities on MRI
Mao et al. (2020), *JAMA Neurology*; Wuhan China; April 10	214 case series, with 78 (36.4%) having neurological manifestation (16 January to 19 February 2020). Severely ill were older, had more comorbidities (esp. hypertension) and fewer typical symptoms (fever, cough).	Severely ill (compared to non-severe) had more neurological symptoms: CVAs (5.7% vs 0.8%), impaired consciousness (14.8% vs 2.4%) and skeletal muscle injury (19.3% vs 4.8%); they also had higher D-dimer levels, indicating a potential coagulopathy
Helms et al. (2020), *NEJM*; France; April 15	Case series of 58 patients presenting to ICU.	84% had neurological signs, 13 had MRI scans of which 8 had leptomeningeal abnormalities
Toscano et al. (2020), *NEJM*; Italy; April 17	Case series of five patients who had Guillain–Barré syndrome following COVID-19 infection.	Initial symptoms (5–10 days after onset of viral illness) were as follows: four patients with lower limb weakness; one with facial diplegia, followed by ataxia and paresthesia. In four patients, flaccid tetraparesis or tetraplegia evolved over 3–4 days. All five tested negative for SARS-CoV-2 in CSF. Three patients had inflammatory changes in nerve roots on MRI

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Table 1. (Continued)

Authors (year), journal; location of study; date	Study type and description	Key findings
Gutiérrez-Ortiz et al. (2020), *Neurology*; Spain; April 17	Case reports of two patients who were COVID-19 positive, presented acutely one with Miller Fisher syndrome and other with polyneuritis cranialis.	One patient presented with anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, albuminocytologic dissociation and the other presented with ageusia, bilateral abducens palsy, areflexia and albuminocytologic dissociation. Normal non-contrast CTs but no MRIs done.
Nathan et al. (2020), *Lancet*; France; April 27	Case series of five COVID-19 positive infants < 3 months of age.	Four showed neurological symptoms on admission – axial hypotonia, drowsiness and/or moaning sounds. CSF was negative for SARS-CoV-2. Rapid recovery within 1–3 days. Infants' parents showed mild signs but were not tested for COVID-19.
Oxley et al. (2020), *NEJM*; USA; April 28	Case series of five patients (all <50 years) presenting with large-vessel stroke who tested positive for COVID-19.	Clinical signs of stroke such as hemiplegia, reduced consciousness, dysphasia and sensory deficits. D-dimer levels significantly elevated.
Alberti et al. (2020), *Neurology*; Italy; April 29	Case report of a single patient with Guillain–Barré syndrome during COVID-19 infection.	71-year-old man presented with acute, severe flaccid tetraparesis 1 week after onset of respiratory symptoms, COVID-19 positive, died of progressive respiratory failure despite high-dose IV Ig and respiratory support.
Beyrouti et al. (2020), *JNNP*; UK; April 30	Case series of six patients presenting with large-vessel stroke who tested positive for COVID-19.	All six had large vessel occlusions in the setting of significantly elevated D-dimers.
Dinkin et al. (2020), *Neurology*; USA; May 1	Case reports of two patients who were COVID-19 positive, both presented with ophthalmoplegias.	One patient presented with left ptosis, left partial oculomotor palsy, bilateral abducens palsies, bilateral distal leg paraesthesias and areflexia. Enhancement of the left oculomotor nerve on MRI. Improved with IV Ig. The other presented with a right abducens nerve palsy, normal CSF and bilateral optic nerve enhancement on MRI.
Von Weyhern et al. (2020), *Lancet*; Germany; June 4	Pathologic reports of autopsies done on six patients who died from COVID-19.	Three patients died of cardiorespiratory failure, one died of pulmonary embolism, two died of intracranial haemorrhage. Five of the patients demonstrated pan-encephalitis and all demonstrated meningitis. In particular, all patients demonstrated perivascular and interstitial encephalitis with neuronal cell loss in brainstem nuclei. Petechial haemorrhages were present in three patients. Brain tissue infection by SARS-CoV-2 could not be established.
Solomon et al. (2020), *NEJM*; USA; June 12	18 COVID-19 deaths, post-mortem findings.	Presenting neurologic symptoms were myalgia (in three patients), headache (in two) and decreased taste (in one). SARS-CoV-2 nucleocapsid protein was present in low levels in brain tissue from five (28%) patients. Brain specimens showed only hypoxic changes and did not show encephalitis or other specific brain changes.
Kanberg et al. (2020), *Neurology*; Sweden; June 16	Case series of 47 patients with mild ($n = 20$), moderate ($n = 9$) or severe ($n = 18$) COVID-19 measuring two plasma biomarkers of CNS injury.	Patients with severe COVID-19 had higher plasma concentrations of glial fibrillary acidic protein (GFAp) and neurofilament light chain protein (NfL).

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Table 1. (Continued)

Authors (year), journal; location of study; date	Study type and description	Key findings
Coolen et al. (2020), *Neurology*; Belgium; June 16	Case series of 19 deceased patients who underwent early post-mortem (<24 hours after death) structural brain MRI.	Parenchymal brain abnormalities were observed in four decedents: subcortical micro- and macro-bleeds (two decedents), cortico-subcortical oedematous changes evocative of posterior reversible encephalopathy syndrome (PRES, one decedent), and nonspecific deep white matter changes (one decedent). Asymmetric olfactory bulbs were found in four decedents.
Varatharaj et al. (2020), *The Lancet Psychiatry*; UK; June 25	Case series of 125 patients presenting with neurological symptoms.	77 patients presented with a cerebrovascular event (57 had an ischaemic stroke, 9 intracerebral haemorrhage and 1 CNS vasculitis). 39 patients had altered mental status: nine with unspecified encephalopathy and seven with encephalitis. The remaining 23 patients with altered mental status fulfilled the clinical case definitions for psychiatric diagnoses, and 21 of these were new diagnoses. Ten of 23 patients with neuropsychiatric disorders had new-onset psychosis, 6 had a neurocognitive (dementia-like) syndrome and 4 had an affective disorder.
Zambreanu et al. (2020), *Journal of Neurology, Neurosurgery, and Psychiatry*; UK; June 29	A case study of a 66-year-old patient who developed limbic encephalitis.	Brain MRI on day 2 of illness revealed non-enhancing, symmetrical T2 and FLAIR hyperintensities in mesial temporal lobes and medial thalami and to a lesser extent upper pons, as well as scattered subcortical white matter hyperintensities. Diffusion scans showed punctate bright signal on the B1000 map in the medial temporal lobes, thalami and fornices.
Abdel-Mannan et al. (2020), *JAMA Neurology*; UK; July 1	Case series of 27 children with COVID-19 paediatric multisystem inflammatory syndrome.	Four patients (14.8%) had new-onset neurological symptoms, including encephalopathy, headaches, brainstem and cerebellar signs, muscle weakness, and reduced reflexes. Brain MRI found splenium signal changes in all four patients. SARS-CoV-2 not present in CSF of two patients who were tested. In all three patients who underwent electroencephalography, a mild excess of slow activity was found. In all three patients who underwent nerve conduction studies and electromyography, mild myopathic and neuropathic changes were seen.
Merkler et al. (2020), *JAMA Neurology*; USA; July 2	Retrospective cohort study of 1916 adult patients with emergency department visits or hospitalisations with COVID-19 from 4 March 2020 through 2 May 2020.	1.6% of COVID-19 patients had an acute ischemic stroke, compared to 3 of 1486 (0.2%) patients with influenza.
Cebrián et al. (2020), *Neurology*; Spain; July 7	A case report of a 74-year-old woman presenting with gastrointestinal symptoms, followed by headache and impaired consciousness.	Neurological examination revealed impaired level of consciousness, photophobic appearance, confusion and incoherent speech. CSF qRT-PCR tests for SARS-CoV-2 were positive. Brain MRI showed a 3 mm area of restricted diffusion.
Paterson et al. (2020), *Brain*; UK; July 8	A case series of 43 patients presenting with neurological disorders.	10 patients had a parainfectious or septic encephalopathy with delirium. 12 patients presented with inflammatory CNS syndromes (2 with encephalitis, 9 with acute demyelinating encephalomyelitis). 8 had ischaemic stroke. 7 patients had Guillain-Barré syndrome.

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Table 1. (Continued)

Authors (year), journal; location of study; date	Study type and description	Key findings
Chougar et al. (2020), *Radiology*; France; July 17	A case series of 73 patients presenting with neurological disorders who underwent MRI scans.	Forty-three patients had pathological MRI findings 2–4 weeks after symptom onset: 17 with acute ischemic infarct, 1 with a deep venous thrombosis, 8 with multiple microhaemorrhages, 22 with perfusion abnormalities, 3 with restricted diffusion foci within the corpus callosum consistent with cytotoxic lesions of the corpus callosum. Multifocal white matter-enhancing lesions were seen in four ICU patients. Basal ganglia abnormalities were seen in four patients. CSF analysis was negative for SARS-CoV-2 in all tested patients ($n = 39$).
Kremer et al. (2020), *Neurology*; France; July 17	A retrospective multicenter study of 64 patients presenting with neurological manifestations who underwent MRI scans.	36 patients (56%) had abnormal neuroimaging. 17 had ischaemic stroke, 8 had encephalitis and 11 had leptomeningeal enhancement. Leptomeningeal enhancement was seen best on post-contrast FLAIR imaging. 25 patients underwent CSF analysis. 13 patients demonstrated markers of inflammation in the CSF. RT-PCR SARS CoV-2 was negative in the CSF of all patients tested ($n = 20$).
Infection in infants and evidence for vertical transmission		
Zhu et al. (2020), *Translational Pediatrics*; China; February 6	Retrospective analysis of clinical features and outcomes of 10 neonates (including 2 twins) born to 9 mothers with confirmed COVID-19 infection.	6 neonates were premature, 2 small for gestational age and 1 large for gestational age. 4 remained in the hospital and 1 died. 9 neonates were tested and all were negative indicating no evidence of vertical transmission.
Schwartz (2020), *Arch of Pathology and Laboratory Medicine*; USA; March 17	Analysed literature describing 38 pregnant women with COVID-19 and their newborns from China.	No maternal deaths in this group unlike SARS and MERS. No confirmed cases of intrauterine transmission. All neonatal specimens tested (including some placentas) were negative using RT-PCR tests. No evidence of vertical transmission.
Dashraath et al. (2020), *American Journal of Obstetrics & Gynecology*; Singapore; March 23	Review of literature which pooled 55 case studies of pregnant women who were COVID-19 positive. Most studies were from China.	No definitive evidence of vertical transmission.
Di Mascio et al. (2020), *American Journal of Obstetrics and Gynecology–Maternal Fetal Medicine*; Italy, UK and Russia; March 25	Systematic review of 19 studies including 79 coronavirus-positive pregnant women, 41 (51.9%) tested positive for COVID-19 and the remainder were MERS or SARS positive.	Coronavirus associated with higher rates of miscarriage (39%), preterm birth (24.3%), premature labour (20.7%), preeclampsia (16.2%), foetal growth restriction (11.7%), caesarean (84%) and perinatal death (11%). In COVID-19-positive cases, the most common adverse outcome was preterm birth (41%), with perinatal death at 7%. Some outcomes for COVID-19 were better than SARS or MERS, incl. rates of ICU admission (9.3% vs 44.6% vs 53.3%), need for mechanical ventilation (5.4% vs 40.9% vs 40%) and maternal death (0% vs 28.6% vs 25.8%). A major limitation of this study was lack of testing of neonates and reports of no vertical transmission was based on clinical features.

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Table 1. (Continued)

Authors (year), journal; location of study; date	Study type and description	Key findings
Dong et al. (2020), *JAMA*; China; March 26	A case report of a COVID-19 positive mother who delivered preterm via caesarean section.	RT-PCR test of swabs done repeatedly over 16 days on neonate were negative. However, SARS-CoV2 IgG and IgM, white blood cells and IL-6 cytokines were elevated and remained so by day 14.
Zeng et al. (2020), *JAMA*; China; March 26	Case series of six pregnant COVID-19 positive mothers, all of whom delivered by caesarean section.	Six neonatal throat swabs showed negative RT-PCR results; however, all six had antibodies in serum. Two of them had significantly raised IgG and IgM concentrations, with the latter possibly indicating passage of the virus through the placenta. Inflammatory cytokine IL-6 was significantly increased in all infants.
Breslin et al. (2020), *American Journal of Obstetrics and Gynecology–Maternal Fetal Medicine*; USA; March 27	Case series of 43 COVID-19 positive pregnant women from a New York hospital, 33% of whom were asymptomatic and identified by universal testing.	No confirmed cases of COVID-19 on testing neonates on day 1 of life.
Karimi-Zarchi et al. (2020), *Fetal Pediatric Pathology*, April 2	A review of 31 COVID-19 positive pregnant mothers.	No COVID-19 detected in neonates or placentas. Two of the mothers died from respiratory complications of COVID-19.
Zamaniyan et al. (2020), *Prenatal Diagnosis*; Iran; April 17	Case report of COVID-19 positive pregnant mother who delivered a neonate preterm via caesarean section.	Neonate had a negative test on day 1. Amniotic fluid and infant PCR test subsequently were positive for COVID-19 infection indicating vertical transmission. Mother died 11 days post delivery due to COVID-19 complications.
Alzamora et al. (2020), *Am J Perinatol*; Peru; April 18	41 year old with diabetes, presented at 33 weeks gestation, with respiratory insufficiency. Tested positive for COVID-19. Developed respiratory failure requiring mechanical ventilation. Emergency Caesarean and immediate isolation of neonate with no skin-to-skin contact with mother.	16 hours post delivery, neonatal nasopharyngeal swab was positive for SARS-CoV-2 RT-PCR. Immunoglobulin (Ig)-M and IgG for SARS-CoV-2 were negative. Maternal IgM and IgG were positive on postpartum day 4 (day 9 post symptom onset). Earliest report of positive PCR in a neonate, suggesting vertical transmission.
Peng et al. (2020), *Journal of Infection and Public Health*; China; May 1	Case report of a preterm neonate born by caesarean section to a COVID-19-positive mother. Mother had foetal intrauterine distress.	Neonate presented with mild respiratory distress and received general management and recovered. A series of SARS-CoV-2 nucleic tests from the neonate from various sites including throat and bronchoalveolar lavage fluid were negative. The nucleic acid test from the mother's amniotic fluid, vaginal secretions, cord blood, placenta, serum, anal swab and breast milk were also negative, indicating no evidence of vertical transmission.
Li et al. (2020), *JAMA Network Open*, China; May 1	Cohort study identifying all males admitted to a hospital for treatment of COVID-19 for just over 2 weeks at the end of January 2020.	38 patients enrolled for semen testing. Six (15.8%) had positive SARS-CoV-2 in semen samples indicating potential for sexual transmission and transmission during pregnancy.
Patanè et al. (2020), *AJOG MFM*; Italy; May 15	Case series of 22 pregnant women with COVID-19 who delivered at a Bergamo hospital.	In 2 of the 22 neonates, nasopharyngeal swab was positive for SARS-CoV-2 RT-PCR. Placental tissue of both mothers also tested positive for SARS-CoV-2 RT-PCR, whereas placental tissue from two mothers with COVID-19 negative neonates did not.

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Table 1. (Continued)

Authors (year), journal; location of study; date	Study type and description	Key findings
Groß et al. (2020), *The Lancet*; Germany; May 25	Case series examining breast milk in 2 nursing mothers with COVID-19.	Breast milk from one mother tested negative for SARS-CoV-2; however, breast milk from the second mother tested positive at days 10, 12 and 13.
Kirtsman et al. (2020), *CMAJ*; Canada; June 15	Case study of a mother and infant dyad with COVID-19. Neonate was born via c-section. Neonate was not in contact with vaginal secretions; the membranes were intact before birth; and there was no skin-to-skin contact with the mother before collection of the first neonatal nasopharyngeal swab.	Neonate's nasopharyngeal swabs were positive for SARS-CoV-2 gene targets via RT-PCR on day of birth, day 2 and day 7. Neonatal plasma tested positive on day 4, and stool was positive on day 7. The mother's nasopharyngeal swab, breast milk and vaginal swab were positive for SARS-CoV-2 RNA. Placenta was positive for SARS-CoV-2 RNA on both the mother and infant sides.
Vivanti et al. (2020), *Nature Communications*; France; July 14	Case study of a neonate born via c-section to a mother infected in the last trimester and presenting with neurological compromise. C-section was performed with intact amniotic membranes, in full isolation, under general anaesthetic.	Clear amniotic fluid was collected prior to rupture of membranes, during c-section and tested positive for both the E and S genes of SARS-CoV-2. At 1.5 hours of life, blood and non-bronchoscopic bronchoalveolar lavage tested positive for the E and S genes of SARS- CoV-2. Nasopharyngeal and rectal swabs collected at 1 hour of life were positive for the two SARS-CoV-2 genes. On the third day of life, the neonate suddenly presented with irritability, poor feeding, axial hypertonia and opisthotonos. CSF was negative for SARS-CoV-2. MRI at 11 days of life showed bilateral gliosis of the deep periventricular and subcortical white matter, with slightly left predominance. RT-PCR on the placenta was positive for both SARS-CoV-2 genes.

MRI: magnetic resonance imaging; FLAIR: fluid attenuated inversion recovery; CT: computed tomography; CSF: cerebrospinal fluid; PCR: polymerase chain reaction; CNS: central nervous system; CVA: cerebrovascular accident; RT-PCR: reverse transcriptase–polymerase chain reaction; ICU: intensive care unit; SARS: Severe Acute Respiratory Syndrome; MERS: Middle-East Respiratory Syndrome; IL: interleukin.

commonly than initially thought and estimates range from 36% to 84% (e.g. Helms et al. and Mao et al., see Table 1). In those with more severe illness, these neurological complications include impaired consciousness, immune-mediated neuropathies, encephalopathies and large-vessel strokes. A recent systematic review (Ghannam et al., 2020) showed that COVID-19-related neurological complications were associated with poorer outcomes or death in 43.9% of cases, with cerebrovascular insults being most prevalent (49%). Of those with cerebrovascular complications, there were raised procoagulation parameters such as D-dimer levels (>80%), C-reactive protein (57%) and fibrinogen (28.5%). Indeed, evidence suggests that thrombosis affecting multiorgan systems is associated with poorer outcomes (Gupta et al., 2020). Importantly, pulmonary thromboses, including in the microvasculature, may also explain the so-called 'happy-hypoxics' (Couzin-Frankel, 2020). Others have suggested that an apparent unconcern regarding low oxygen levels results from viral CNS involvement of the medullary cardiorespiratory centre (Li et al., 2020b).

Encephalopathy in COVID-19 may be a direct viral effect due to neuroinvasion, an immune-mediated pathology triggered by the virus, indirect immunopathology due to blood–brain barrier dysfunction, or a combination of all three. A recent COVID-19 postmortem study identified evidence of inflammation and neuronal loss but did not confirm virus infiltration (Von Weyhern et al., see Table 1). Magnetic resonance imaging (MRI) in COVID-19 patients may allow early identification of neurological involvement or allow differentiation of true neurological involvement from toxic and metabolic CNS effects in severely affected COVID-19 patients. Lumbar puncture CSF examinations have tended to give negative results (Table 1), but should be considered in severe cases. Only one study mentioned the presence of a dysexecutive syndrome, though the measures used were rudimentary (Helms et al., see Table 1). It is likely that neurological and possible neuropsychiatric complications will become clearer as more patients recover.

Early reports of increasing mental health problems following COVID-19 infections have been further substantiated by a systematic review (Rogers et al., 2020) reporting an increased incidence of depression, anxiety, fatigue and insomnia following coronavirus infections. The findings were limited by poor methodological issues due to lack of pre-infection assessments and lack of control groups.

Intriguingly, there is emergence of more complex neuropsychiatric symptoms such as changes in behaviour and psychosis in those who are COVID-19 positive. Therefore, it will be imperative to systematically document frontline clinician observations of neurological and neuropsychiatric sequelae and to follow such cases longitudinally. CNS effects involving disrupted behaviour and cognition in affected adults and children (particularly during critical periods of childhood maturation and adolescence) may later lead to mental disorders with long-term sequelae.

SARS-CoV-2 mechanisms for neural injury – how animal models inform treatment strategies

Mammalian studies indicate SARS-CoV-2 is similar to other coronaviruses and enters the cell via ACE2 receptors after priming by transmembrane serine protease 2 (TMPRSS2) targeting the viral spike (S) protein (Hoffmann et al., 2020). Limited data indicate genetic variations in ACE2 and TMPRSS2 may be important in variable susceptibility to SARS-CoV-2, across ethnicities and gender (with higher expression in men). Neural injury caused by COVID-19 may result from direct neuronal invasion, haematogenous entry (virus-containing immune cells) or secondary to local and systemic inflammatory changes. ACE2 binding affinity for SARS-CoV-2 is 10-fold higher compared to SARS-CoV despite it using a conserved mechanism, highlighting its enhanced infectivity and transmissibility. In the CNS, ACE2 receptors are expressed in the spinal cord, cortex, hippocampus, cerebellum and other brain regions. However, serine protease TMPRSS2, which is also required for SARS-CoV-2 entry to cells, is only weakly expressed in brain (Uhlén et al., 2015). Furthermore, ACE2 and TMPRSS2 showed substantial co-expression in the olfactory epithelium compared to olfactory neuronal cells (Kerslake et al., 2020). While more studies need to examine the issue of direct viral effects on the CNS, these findings might suggest that direct viral infiltration is not be the main mechanism of CNS damage. Rather, the majority of CNS complications may result from secondary mechanisms, such as respiratory distress, hypoxia, thrombosis and neuroinflammation.

Animal studies may inform our understanding of the pathophysiology of CNS involvement in SARS-CoV-2 infections, in addition to human cellular models that are being developed. Mice, hamsters, ferrets and non-human primates have been used, with mice as the most pragmatic preclinical models (Cockrell et al., 2018). Mice transgenic for the human ACE2 (hACE2) gene, encoding the primary SARS-CoV receptor, represent a useful tool as they are susceptible to the virus. Potential treatment strategies in these animal models include targeting pre-treatment with pan-coronavirus fusion inhibitors and inhibitors of TMPRSS2. ACE2 downregulation secondary to SARS-CoV-2 viral spike (S) protein binding is one mechanism that may contribute to neuroinflammation (Hoffmann et al., 2020), as well as inflammation in other organs including lung and heart, with recombinant ACE2 able to ameliorate tissue injury. ACE2 is an important part of the renin–angiotensin system (RAS) responsible for metabolising Ang II to Ang-(1-7), with the latter providing a

sympatholytic and antihypertensive effect that is protective in neuronal injury. Dysregulation of this system in COVID-19 infection contributes to ischemic brain injury by promoting small-vessel hypoperfusion and arterial atherothrombosis.

Severe COVID-19 infection leads to activation of microglia and macrophages with release of cytokines and chemokines, which may explain the hyperactive immune response observed. The resultant systemic increase in pro-inflammatory cytokines may contribute to presenting symptoms of headache, arthralgia and fever and in more severe cases to delirium, paresis and seizures. These systemic inflammatory and pro-coagulant changes in SARS-CoV-2 infection will vary with host factors such as ACE2 receptor expression, vascular risk factors and prothrombotic states. ACE2 receptor gene expression is lower in males and decreases with age and diabetes (Brufsky, 2020). These factors will exacerbate the downregulation of ACE2 by SARS-CoV-2 binding and correlate with severity of illness and mortality.

Alterations in the coagulation pathway are common in SARS-CoV-2 infection, portend a poor prognosis and likely represent the crossroads between the coagulation pathway and the immune response. Elevated D-dimer (indicative of fibrinolysis), prolonged prothrombin time with a preserved activated partial thromboplastin time (APTT) and elevated fibrinogen are most commonly observed. The coagulation changes reflect inflammation-induced changes in endothelial cells (which express ACE2), endotheliitis secondary to viral infection and result in capillary microthrombi that may cause small-vessel ischemic change in organs, such as lungs and brain. In severe infection, large vessel arterial occlusion-led stroke can affect multiple territories with evidence of positive lupus anticoagulant in five of six patients with stroke (Beyrouti et al., see Table 1); however, the criteria for antiphospholipid syndrome, an autoimmune hypercoagulable state, were not met and the pathogenic role of this inhibitor was unclear. The overlapping host inflammatory response and inflammatory milieu created by SARS-CoV-2 induced low ACE2, and reduced host mobility because of the illness, are likely to contribute to the increased cases with cerebral, pulmonary and other organ thromboses.

Vertical transmission, maternal immune activation and intergenerational impact

The global nature of the COVID-19 pandemic raised concern for pregnant women across the world regarding the outcomes of SARS-CoV-2 infections, as the effects on mothers and foetuses (including long-term neurodevelopmental impacts) are largely unknown.

There are three main considerations for a developing foetus: (1) vertical transmission of the disease from the mother, (2) the prenatal effects of maternal systemic infection on the foetus, and (3) the possible effects on placental functioning and consequent pregnancy outcomes. The presence of ACE2 receptors in the placenta suggests potential for such transmission. Details of studies reporting on this issue are outlined in Table 1, with some initial studies reporting no evidence of vertical transmission and some reports of positive cases in neonates emerging more recently.

Most studies addressing this issue are case reports or case series, as would be expected for a disease that has affected humanity for less than a year, while some have attempted systematic reviews and meta-analyses trying to incorporate heterogeneous methods and findings. One such meta-analysis of 108 pregnancies (Zaigham and Andersson, 2020) concluded that vertical transmission could not be excluded. While most such studies did not include testing for coronavirus, those that included testing suggest this possibility. Several studies have found that reverse transcriptase–polymerase chain reaction (RT-PCR) tests produced positive results in the infant. While some studies did not find evidence for a positive test, they did identify elevated cytokines, particularly interleukin (IL)-6 as well as IgM and IgG antibodies (summarised in Table 1). While IgG antibodies and cytokines may passively cross the placental barrier, IgM due to its larger molecular structure usually does not, which indicates antibodies were likely produced by the infant in response to in utero SARS-CoV-2 infection. These findings (although only case reports) may suggest that foetal infection with SARS-CoV-2 had occurred earlier in pregnancy, resulting in the foetus developing antibodies. Furthermore, one French study by Nathan and colleagues (see Table 1) reported five infants below age 3 months with confirmed COVID-19 presenting with neurological symptoms, raising important questions about how they became infected. Although their parents showed symptoms of mild infection they were unfortunately not tested.

Irrespective of vertical transmission, maternal infection could lead to neurodevelopmental changes in the foetus. Schizophrenia incidence rates have risen following previous influenza epidemics and a range of viral and bacterial maternal infections are associated with neurodevelopmental abnormalities in the offspring, especially with infection in early pregnancy (Meyer, 2019). These infections potentially trigger maternal immune systems releasing a cascade of cytokines and chemokines (e.g. tumour necrosis factor [TNF]-a, IL-6) and other immune alterations that may be transmitted to the foetus. Also, critically ill pregnant women are at risk of placental hypoxia, compromising foetal oxygen supply that can lead to restricted growth and arrested brain development.

We also have a greater understanding from clinical and preclinical models such as maternal immune activation (MIA) in rodents that maternal neuroinflammatory challenges (e.g. with

influenza viruses), particularly during critical trimesters, can lead to significant neurodevelopmental changes in the foetus and alter neurodevelopmental trajectories (Meyer, 2019). Such preclinical models have informed the pathogenic mechanisms of various neurodevelopmental disorders, particularly schizophrenia and autism spectrum disorder (ASD). As observed in these models of maternal infection, similar increases in cytokines are also observed during coronavirus infection, and these factors could contribute to increasing vulnerability and predisposition to mental illnesses in the years to come.

A number of viruses are known to affect the developing foetus. A recent review (Yockey et al., 2020) summarises the mechanisms involved, including effects relevant to each trimester, direct effects of viruses reaching the foetus and impact of maternal and foetal immune activation. A number of risk factors are described by Meyer (2019) relevant to immune activation including low maternal iron and anaemia, gestational diabetes and maternal stress, which raise important issues in relation to COVID-19 infection in pregnancy. While the available evidence suggests there are no gross abnormalities in neonates of mothers who were COVID-19 positive (cf. Zika and cytomegalovirus), more data are needed.

Furthermore, long-term effects in these children may not be evident for years, particularly as the peak incidence for many psychiatric disorders with neurodevelopmental origins is in late teens or early adulthood. This hypothesis is currently speculative; extensive evidence from other viral infections affecting pregnancy and offspring outcomes suggests that appropriate longitudinal cohort studies and preclinical models need to be established. Animal models provide viable tools, with shorter time frames for their developmental trajectories, which could provide a 'fast-forward' view of potential impacts on future generations. These intergenerational and possibly transgenerational propagative effects could include a range of phenotypic impacts including increased predisposition to neurological, neuropsychiatric and neurodevelopmental disorders.

While there is justifiable focus on maternal infection, evidence from at least one other infectious disease indicates the potential intergenerational epigenetic effects of paternal infection. The first evidence that a pathogenic infection preconception (*Toxoplasma gondii*) in males can induce phenotypic changes in offspring was recently generated in a mouse model (Tyebji et al., 2020) and the impacts on behaviour were both intergenerational (affecting offspring) and transgenerational (affecting grandoffspring). A recent publication (Table 1) has detected SARS-CoV-2 presence in semen samples suggesting the possibility of transmission from paternal infection to offspring.

Further high-quality studies evaluating the effects of maternal and paternal infection on the offspring and establishing clinical cohort studies to follow up this population would be essential in understanding the risks SARS-CoV-2 poses. Such research could inform prevention and treatment of negative intergenerational impacts on offspring.

Treatment strategies

The field is racing to identify promising treatments and vaccines. Treatments relevant to neurological and neuropsychiatric sequelae could include dealing with severe inflammatory responses, thromboses and underlying comorbidities (including hypertension and diabetes). While a review of these treatments is beyond the scope of this article, further information relevant to current approaches to treatments has been established by the NC-IUPHAR (the nomenclature committee of the International Union of Basic & Clinical Pharmacology; www.guidetopharmacology.org/coronavirus.jsp) and an up-to-date list of current trials can be found at the ClinicalTrials.Gov website (https://bit.ly/2SkDe7Q).

Conclusions and ways forward (Box 1)

As COVID-19 cases increase globally and lockdown measures ease across many countries, we are already witnessing 'second waves' of infection. It is imperative that we utilise collaborative networks to systematically document neurological and neuropsychiatric clinical manifestations of patients with COVID-19 (e.g. *Coro*NerveStudies Group), which will assist in managing the illness longer term, as proposed by colleagues (Holmes et al., 2020) who mapped out the research priorities for the pandemic. This includes characterising clinical phenotypes, short- and long-term sequelae, response to treatments and ultimately the morbidity and mortality caused by CNS involvement. Detection of COVID-19 viral signatures in autopsies and brain tissue sampling will conclusively establish the effects of the virus on the CNS. Imaging will play a key defining role in providing diagnostic precision and/or early detection of neurological manifestations, assisting treatment decisions and improving understanding of pathogenesis.

Observations of unusual behavioural and psychiatric symptoms in those recovering will also be important. If the virus enters the CNS via the olfactory nerve or other routes, which is not clearly established at this stage, it has the potential to cause neuropsychiatric and neurological complications. This may include loss of inhibitory control, apparent unconcern, loss of normal fear and anxiety, and social disinhibition. Cognitively, we might expect impacts on inhibitory control systems, executive functions and memory. Anecdotal evidence from reports by clinicians (mainly general practitioners) suggests such behaviours were observed, especially an apparent lack of concern or appreciation of the seriousness of symptoms, leading to sudden death in some

Box 1. Summary and ways forward.

Key findings
Anosmia and ageusia are important early signs of infection, often before other respiratory symptoms.
Neurological manifestations of COVID-19 infection are increasingly reported.
Thromboses may be secondary to a severe inflammatory response, resulting in strokes and other thrombotic events in multiple organs.
Behavioural and cognitive changes may be secondary to CNS involvement, but require longitudinal study.
Possible vertical transmission. RT-PCR tests in neonates may be negative especially if infection occurred days to weeks prior to birth; however, antibody testing may be key to infection identification.
Maternal and possible paternal transmission needs further exploration.

Limitations
Rapid publications, cross-sectional or retrospective data limited, poor methodological quality and rigour make generalisability difficult.
Limited testing and detection underestimate prevalence of neurological and neuropsychiatric complications.
Lack of adequate data on vertical transmission and possible neurodevelopmental impacts.
Lack of data in high-risk groups, including severely mentally ill and those with disability.

Ways forward
Establishing database resources to gather reports in the first instance.
- CoroNerve surveillance survey established in the United Kingdom (www.rcpsych.ac.uk/members/your-faculties/neuropsychiatry/coronerve-surveillance-survey).
- Resource being established in Australia.

Establishing cohorts to be followed longitudinally.
- Including behavioural, cognitive and imaging analysis.
- Recruitment of cohorts of adults and children to assess neurodevelopmental impacts.

Postmortem brain bank of positive cases to assess impact of the virus on the CNS.
Testing for SARS-CoV-2 is a critical factor in determining relevance of these and other symptoms.

CNS: central nervous system; RT-PCR: reverse transcriptase–polymerase chain reaction; SARS: Severe Acute Respiratory Syndrome.

patients. This raises important questions about possible direct CNS effects and their likely role in the high mortality observed.

The fact that the spatial and temporal progress of this pandemic has been mapped in unprecedented detail will allow the establishment of crucial longitudinal studies, including birth cohorts. Thus, it will be important to closely monitor the outcomes of children born to mothers infected prior to, and during, pregnancy. Furthermore, we suggest that the health outcomes of children whose fathers were infected prior to conception should also be monitored. Coronaviruses belong to a large family with extensive animal reservoirs and potential to make the leap to humans. This is unlikely to be the last pandemic humanity has faced and future pandemics caused by viruses (and other pathogens) with higher infectivity and mortality may be even more severe. Initiatives such as the Coalition for Epidemic Preparedness Innovations (CEPI) and other concerted international research efforts must be maintained, fully resourced and supported if we are to gain an advantage in this battle to protect, and optimise, global health and prosperity.

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Supplemental Material

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