



Coronavirus 2019: clinical and neuropathological aspects

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Purpose of review

To understand the role of postinfectious autoimmune vascular inflammation in the pathogenesis of coronavirus disease 2019-related neurological illness caused by the novel severe acute respiratory syndrome coronavirus 2 virus and its effects on the brain in children and adults.

Recent findings

There are a very small number of postmortem neuropathological series of coronavirus disease 2019-related cerebrovascular and parenchymal disease. However, they fall into at least three major categories, with the majority manifesting those of terminal hypoxia, and others demonstrating inflammatory vascular leptomeningeal, cerebral and brainstem interstitial changes suspicious for encephalitis in a minority of cases. It remains uncertain whether these histopathological features have a relationship to post-infectious inflammatory immune mechanisms and microscopic vasculitis in adults as it appears to be in affected children with multisystem inflammatory syndrome.

Summary

The reasons for this dichotomy are unclear but may related to inherent and epigenetic factors that remain poorly understood. Treatment addressing postinfectious mechanisms of pulmonary, systemic, and nervous system injury may avert early mortality.

Keywords

autoimmunity, coronavirus disease 2019, neurological disease, pediatric multisystem inflammatory syndrome, severe acute respiratory syndrome coronavirus 2, vasculitis

INTRODUCTION

The earliest reports of clusters of patients with pneumonia of unknown origin linked to exposure at a seafood and wet animal market in Wuhan (Hubei Province, China) [1[■]] were rapidly identified as a new beta coronavirus named severe or novel acute respiratory syndrome-coronavirus-2 (SARS-nCoV-2 or SARS-CoV-2). These single-stranded RNA enveloped viruses have the largest known RNA genome, ranging from 26.2 to 31.7 kilobases that encodes an important spike glycoprotein that mediates viral entry and determines the range of potential host-cell tropism and disease pathogenesis, hence it has been a major source of vaccine interest [2]. Six coronavirus species cause human disease [3] types widely prevalent in the population that are associated with the common cold symptoms and two others, severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), the causal agent of the SARS outbreaks in 2002 and 2003 of Guangdong Province, China [4], and the Middle East Respiratory Syndrome or Middle East respiratory syndrome coronavirus (MERS-CoV), responsible for outbreaks in 2012

[5] are zoonotic beta coronaviruses and linked to fatal illness [6]. SARS-CoV-1 and SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE 2) receptor binding site to infect ciliated bronchial epithelial cells and type II pneumocystis, which explains the affinity of pulmonary involvement.

EPIDEMIOLOGY

With five of seven human coronavirus isolated in this century, coronaviruses have assumed an important place in 21st century [7]. SARS-CoV-2 also originated in bats and reached humans via badgers, Himalayan palm civets and raccoon dogs, showing a similar capacity to infect humans, first by jumping

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KEY POINTS

- Novel coronaviruses are likely continue to proliferate.
- With them comes the foreseeable risk of rising fatality and neurological complications.
- Adults with severe acute respiratory syndrome coronavirus 1 and the coronavirus disease 2 have shown CNS inflammatory vasculopathy but not frank vasculitis.
- Children with multisystem inflammatory syndrome appear to be a heightened risk for Kawasaki disease.
- Immunotherapy aims at modulating or preventing a postinfectious autoimmune inflammatory response.
- Long-awaited vaccination for severe acute respiratory syndrome-coronavirus-2 is underway in different platforms but may pose uncertain risks in healthy recipients and others with asymptomatic infection.

across species from bat reservoirs. A decade later, MERS-CoV originated in bats utilizing camels as intermediate hosts to human. A zoonotic origin of SARS-CoV-2 was confirmed with viral isolation from reservoirs in bats that infected, as intermediate hosts, the Malayan pangolin and other wildlife used for food in China [8,9]. All three outbreaks confirm the high infectivity and lethality of the coronaviruses and the serious public health threat they pose.

There are animal models that convincingly demonstrate the capacity of coronaviruses to enter the central nervous system (CNS) across the blood brain barrier (BBB). Older immunodeficient BALB/c mice exhibit a clinical syndrome, with increasing age as a risk factor [10]. Transgenic K18-hACE2 mice infected with SARS-CoV [11] invoke infiltration of macrophages and lymphocytes to the lungs and a local release of proinflammatory cytokines reminiscent of the cytokine storm postulated in SARS-CoV-2.

An analysis of 425 initial cases of coronavirus (2019-CoV)-infected pneumonia of the Wuhan, Hubei Province of China, from December 2019 to January 2020 lends understanding of the associated epidemiology [12]. Early laboratory confirmed cases of were identified through surveillance of pneumonia of unknown cause with fever ($\geq 38^\circ\text{C}$), radiographic evidence of pneumonia, low or normal white-cell count or low lymphocyte count, and no symptomatic improvement after antimicrobial treatment for 3–5 days after standard therapy; and substantiated by WHO laboratory assays [13] that extracted 2019-CoV RNA by real-time PCR (RT-PCR) using specific primers and probes in upper and lower respiratory tract specimens. Epidemic curves showed an exponential growth rate of 0.10/day

[95% confidence interval (CI), 0.050–0.16] with a doubling time of 7.4 days (95% CI, 4.2–14) and a reproductive rate (R_0) of 2.2 (95% CI, 1.4–3.9), meaning that on average, each patient is spread infection to 2.2 others. The goal of control measures is now to reduce the reproductive number to less than 1 to prevent exponential growth by interrupting human-to-human transmission in small communities through quarantining, careful infection control; tracing, testing and isolation of affected contacts, and use of social distancing and facial masks in the general population.

SUSCEPTIBILITY TO INFECTION

Adults

All individuals are generally susceptible to coronavirus disease 2019 (Covid-19). A convenience sampling of Chinese individuals returning to work from Covid-19 [14] identified females, the elderly, residents with chronic diseases, and children as perceived higher risk and in need of special attention in healthcare management. In small case series, the clinical characteristics of pregnant women with confirmed Covid-19 infection are similar to non-pregnant adult but may be more susceptible to infection versus the general population [15] and should have greater health counseling, screening, and follow-ups to ensure maternal and fetal safety. The risk of severe infection and mortality increases with age, and mortality heightens by comorbid cardiovascular disease, hypertension, diabetes, pulmonary disease, and cancer.

A multicenter retrospective Cox-proportional-hazards regression analysis of 147 critically ill Chinese patients with Covid-19 [16] revealed that age older than 65 years, thrombocytopenia at ICU admission, acute respiratory distress syndrome (ARDS), and acute kidney injury independently predicted higher 60-day mortality. Epidemiological data reflect lower susceptibility among children compared with adults, and milder severity of disease compared to adults however, the large proportion of asymptomatic children makes epidemic surveillance more difficult.

Children

The susceptibility of children to SARS-CoV-2 infection and development of Covid-19 illness is uncertain however; one particularly severe affliction has been noted. Incident cases of fever and mucocutaneous manifestations resembling Kawasaki disease [17], a rare vasculitis of childhood that causes coronary-artery aneurysms, emerged in Europe [18] during school closures after UK pediatricians alerted

the National Health Service to an unusual inflammatory illness. Two contemporaneous reports in the *New England Journal of Medicine* describe the epidemiology and clinical features of the US disorder [19²²,20]. With approximately 1000 cases of so-called multisystem inflammatory disorder in children (MIS-C) worldwide, the incidence is considerably lower than SARS-CoV-2 for individuals less than 21 years of age. Epidemic curves of laboratory-confirmed SARS-CoV-2 infection among persons less than 21 years of age in New York State show a peak in the number of MIS-C cases that follows the peak in the number of laboratory-confirmed SARS-CoV-2 infections by 31 days (from March to 10 May 2020), with an incidence of 322 in 100 000 persons compared with two per 100 000 cases of MIS-C for the same age of less than 21 years [19²²]. Among children with laboratory confirmed MIS-C manifesting prototypical febrile hyperinflammatory syndrome of dermatologic, mucocutaneous, gastrointestinal manifestations and cardiac dysfunction, 48% of patients 0–5 years of age, 43% of patients 6–12 years of age, and 12% of those 13–20 years of age present with typical or suggestive of Kawasaki disease (KD). In view of the overlapping clinical features and the lack of a diagnostic test for either KD or MIS-C, attributing a causal relationship remains enigmatic for several reasons. First, the epidemiology of the two disorders does not follow the same trend in all cases. While KD has been virtually identical in all countries in the world for the past 50 years or more, with 80% of cases occurring in children <5 years of age and with a peak incidence at ~10 months of age, MIS-C typically affects older children. Second, although SARS-CoV-2 is not a definite cause of MIS-C, the appearance of MIS-C during outbreaks of COVID-19 in Europe and the US, although not Asia, is highly suggestive. Third, although children with MIS-C may display some of the clinical features of KD such as fever, dilation of conjunctival blood vessels, rash and redness of the oropharynx, they are not specific for any one diagnosis and can be observed in other childhood infectious diseases. Yet, while the etiology of KD remains largely elusive, there is mounting interest in identifying infectious agents that trigger the cascade that causes the observed cytokine storm with high serum IL-6 levels, coronary aneurysms, and necessary inotropic support to maintain cardiac output and avert shock. The question therefore remains whether MIS-C and KD are the same entity and if SARS-CoV-2 viral infection is one trigger among many for KD. There is a trial recruiting for the collection of clinical data and tissue samples to characterize MIS-C and its relationship to KD (ClinicalTrials.gov Identifier: NCT04538495).

NEUROLOGICAL MANIFESTATIONS AND COMPLICATIONS

The neurologic manifestations of SARS-CoV-2 infection results from a variety of mechanisms including virus-induced hyperinflammatory and hypercoagulable states, and direct virus infection of neurons. There is still a paucity of rigorous case observations of acute, subacute and chronic clinical and laboratory neurological involvement in SARS-CoV-2 infection. Three large case series totaling 425 hospitalized patients illustrate the current state of knowledge including 214 retrospectively studied cases from January to February 2020 in China's Wuhan Province [21]; 58 prospectively studied Covid-19 cases between March and April 2020 in France [22]; and 153 cases surveyed during April 2020 in the United Kingdom [23]. The retrospective, observational study of Wuhan cases was carried out at three centers early in the pandemic [21] noting 36.4% CNS manifestations among them dizziness (16.8%) and headache (13.1%); and 8.9% overall peripheral nervous system manifestations affecting taste (5.6%) and smell (5.1%). There was no mention of brain neuroimaging, lumbar cerebrospinal fluid (CSF) analysis, neuromuscular biopsy findings, or the prognostic contribution to mortality of any particular neurological syndrome.

Among the 58 consecutive French patients seen somewhat later in the pandemic at one hospital with Covid-19-related ARDS [22], investigators noted neurological manifestations in 84%, including encephalopathy, prominent agitation, confusion and corticospinal tract signs each in two-thirds of cases. Two of 13 patients who underwent brain MRI had single acute ischemic strokes, and 13 showed perfusion abnormalities with leptomeningeal involvement in two-thirds. Nonspecific findings seen on electroencephalography suggested encephalopathy. Examination of CSF samples obtained from seven patients showed no cells; two patients had oligoclonal bands identical to electrophoretic serum patterns; and all were negative for SARS-CoV-2 by RT-PCR assay.

Among 153 UK patients enrolled in a surveillance study of the acute neurological and psychiatric complications of Covid-19 in the month of April 2020 [23], two-thirds (62%) of patients overall presented with a cerebrovascular event including stroke (74%), intracerebral hemorrhage (12%), and CNS vasculitis (1%); and a third of patients presented with mental status changes that included encephalopathy (23%) and encephalitis (18%), and the remainder (59%) suggested new presentation of psychosis, dementia, and affective disorder. Altered mental status was the second most common neurological manifestation, affecting patients both older

and younger than age 60 years, while the commonest neurological presentation, that of acute cerebrovascular events, preferentially affected older individuals more often than younger counterparts (82 versus 18%).

CLINICOPATHOLOGICAL CORRELATION

Severe acute respiratory syndrome coronavirus 1

Cases of the 2002 SARS-CoV-1 epidemic have shown neurological manifestations including seizures and encephalitis [24,25]. Complementing these reports, among four patients who died suddenly of dissecting aneurysms, ectopic pregnancy, and cerebral hemorrhage [26] there was positive staining by murine mAbs specific for SARS-CoV-1 nucleoprotein and probes specific for a SARS-CoV-1 RNA polymerase gene fragment for immunohistochemistry. In-situ hybridization of the cerebrum at postmortem included localized perivasculitis of cerebral veins.

Middle East respiratory syndrome coronavirus

There are no published data regarding human post-mortem neuropathological findings of MERS-CoV yet the disorder is still a relevant threat for populations in the Middle East with high lethality (close to 35%) [27]. However, three reported living patients manifested initial fever followed by coma, ataxia, focal motor deficits, and peripheral nerve symptoms [28¹¹] and four of 23 other patients treated at a single hospital reported delayed neurological symptoms up to 3 weeks consistent with concomitant Bickerstaff's encephalitis overlapping with Guillain-Barré syndrome, ICU-acquired weakness, and toxic or infectious neuropathies [29¹¹].

Severe acute respiratory syndrome-coronavirus-2

The postmortem findings of Covid-19 illness have been described in 391 patients succumbing to Covid-19 illness [30¹¹-32¹¹,33,34¹¹,35¹¹,36-50,41], which is miniscule in relation to the number of confirmed cases and reported deaths in the United States and worldwide. Nevertheless, they are both very revealing and important in understanding the likely pathogenic mechanisms associated with SARS-CoV-2 infection. What was initially thought to be a self-limited disease almost exclusively involving the lungs now is being recognized as one that involves multiple organ systems including the brain with the unique capacity for both invasive and post-infectious dysimmune phases that evolve

in an overlapping fashion over a relatively short period.

Younger (51) recently summarized the neuropathological findings of Covid-19 illness in the first 50 cases with detailed brain findings [30¹¹-32¹¹,33,34¹¹,35¹¹]. Older age, male gender, increased serum cytokine and pro-coagulation markers, and critical care hospitalization for ≤ 10 days prior to death characterized the cohort [49]. Serum cytokine and procoagulant were consistently elevated in those so studied. The vast majority of patients were critically ill and managed in an intensive care unit (ICU) where the immediate causes of death was generally ascribed to cardiopulmonary failure. SARS-CoV-2 staining in brain tissue by polymerase chain reaction was negative in all cases [31¹¹,32¹¹,34¹¹,35¹¹], while a third of cases (36%) (30-34) showed focal or diffuse cortical and brain leptomeningeal or interstitial inflammation, characterized mainly as T-cell-mediated based upon flow cytometry. Six patients [32¹¹] between the ages of 58 and 82 years, who presented with somnolence (in 3 with an average Glasgow Coma Scale [GCS] of 11.3) or no neurological symptoms and a normal GCS of 15), (in the other 3) without preponderant comorbidities, showed histopathological features of encephalitis. These included localized perivascular and interstitial infiltrates with neuronal cell loss and axonal degeneration involving brainstem nuclei and tracts without territorial infarctions, or evidence of virus infiltration. Sparse T-cell infiltrates with clusters of macrophages and axonal injury tracking along vessels resembling acute disseminated encephalomyelitis (ADEM) were noted in two other cases, including one with neuronophagia and microglial nodules [34¹¹], and another with expression of angiotensin converting enzyme (ACE)2 receptor along capillary endothelial cells [31¹¹].

Younger's analysis [51] of critically ill Covid-19 cases reveal several important findings and implications. First, hypoxia-ischemia evident does not account for all relevant neuropathological features of severe Covid-19. Second, patients presenting with elevated levels of circulating interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)- α , suggests activation of innate and adaptive immunity indicative of a cytokine storm. Together with increased serum D-dimer and markers of hypercoagulability in 42% of cases, affected patients are at risk for thrombotic and hemorrhagic parenchymal tissue infarction so noted in nine (18%) of cases. Third, the findings of 16% of cases with ADEM-like features or indolent brainstem encephalitis suggests the need for a high index of suspicion in patients presenting with altered sensorium, early brainstem signs including those with fluctuating vital signs and early ventilator dependence.

There were several limitations of this small cohort analysis of literature cases. First, case series were often small and unselected often with missing demographic data and causes of death. Second, there were often contradictory conclusions about the significance of inflammatory vascular brain changes; moreover, there were all critically ill patients and there were no comparisons to control patients with sepsis. Third, it was uncertain whether negative in-situ SARS-CoV-2 RNA PCR results in those so studied makes a secondary inflammatory immune mechanisms of injury more likely.

An updated clinicopathologic analysis of 141 Covid-19 cases shown in Table 1 that comprised 91 additional cases, including 31 cases [39,40] excluded from the series of Younger [51] for lack of description neuropathology, and 60 histopathologically documented cases [36–38] show four notable findings.

The first was the increased number of positive SARS-CoV-2 genome by PCR testing, accounting for 13 (48%) of 27 examined brains in the study by Matschke and colleagues [36]; in 4 (80%) of 5 brain tissue specimens studied by Hanley and coworkers [37]; and in 8 (38%) of 21 brain specimens examined by Puelles and coinvestigators [40]. Remarkably, SARS-CoV-2 presence did not correlate with the severity of neuropathological findings [36]. It remains unclear whether a comparably low viral genome levels detectable by qRT-PCR in brain tissue could be blood-derived.

A second finding was the increase in leptomeningeal and interstitial brainstem inflammation characterized as cytotoxic T-cells in 34 (79%) cases according to Matschke and colleagues [36], coinciding with the localization of SARS-CoV-2 viral proteins in cranial nerves and interstitial areas of the lower brainstem. The detection of SARS-CoV-2 RNA specifically in olfactory bulb neurons and glial cells in 4 (57%) of 7 patients in another study cohort [38], but not in any other brain regions, lends support to a route of viral entry via the olfactory system and the importance of anosmia as an early clinical sign of Covid-19. While activated microglia localize to the olfactory bulb and medulla oblongata in Covid-19 brain tissues suggesting a point of viral entry, similar findings noted in control brains of patients who deceased under septic condition [38]. Considering the capability of SARS-CoV-2 to infect human gastrointestinal enterocytes as well as pneumocytes, it bears consideration whether the vagus nerve derived from the medulla could be another route of entry to the brain.

A third finding was the detection of microglial activation and sparse perivascular and leptomeningeal T-cell infiltrates in Covid-19 brains, as well as in controls with sepsis or systemic inflammation in a

small series [38] suggesting a histopathological correlate of critical illness-related encephalopathy rather than a disease-specific finding.

Fourth, Matschke and colleagues [36] were interested in the neuronal cell types prone to SARS-CoV-2 infection, thereby screening gene expression datasets for signatures related to viral entry and persistence. The authors noted high expression of ACE2 in oligodendrocytes, and increased expression of transmembrane serine proteases 2 and 4 (TMPRSS2 and TMPRSS4) in neurons that respectively encode proteins implicated in host viral entry (ACE2) and pruning of the viral-decorating spikes (TMPRSS2).

There are several implications of these findings in regards the immunoinflammatory and neurotoxic response of SARS-CoV-2 to neurons that has recently been captured in a study by Ramani and coworkers [52] who employed a brain organoid model to examine whether SARS-CoV-2 directly targets neurons and can lead to productive infection and neurotoxicity. Cells from mock organoids displayed a healthy nucleus that is labelled with 4',6-diamidino-2-phenylindole (DAPI) compared to SARS-CoV-2 exposed organoids that display increased terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) which detects the DNA breaks formed when DNA fragmentation occurs in the last phase of apoptosis. While most of the SARS-CoV-2-positive cells are TUNEL-positive, some were caspase-positive displaying pT231 Tau localization at the cell soma not observed in mock organoids. pT231-tau is highly neurotoxic and acts as an early driver of tauopathy in neurodegenerative diseases such as Alzheimer disease. This model offers insight into the fore mentioned findings in the most recent Covid-19 series. For example, if neurons are indeed a target for SARS-CoV-2, a basal (low) level of ACE2 expression may be sufficient for viral entry into neurons. This could explain why SARS-CoV-2 has a broad spectrum of target organs and cell types as suggested by Puelles and colleagues [40]. In so much as Tau abnormalities in SARS-CoV-2 positive neurons could result from infection, it could also result from triggering of a cascade of downstream effects that results in immune-inflammation, neuronal stress, and direct neurotoxicity, all of which warrant future investigations. Moreover, as organoids are an experimentally tractable human in vitro system and convenient to culture as well as infection, organoid models can serve as a test-bed for anti-SARS-CoV-2 therapeutic agents.

Immunotherapy

The Covid-19 pandemic is proving to be associated with high-case fatalities in both children and adults

Table 1. Updated clinical and neuropathologic findings of 141 Covid-19 fatalities

Observation	Number of cases	Reference
Sex		
Male	72	[28 ^{***} ,32 ^{***} ,33,34 ^{***} ,36,38]
Female	31	[28 ^{***} ,30 ^{***} ,31 ^{***} ,33,34 ^{***} ,36]
Age		
<21	0	
1–49	1	[33]
50–64	17	[30 ^{***} ,33,34 ^{***} ,36]
>65	66	[29 ^{***} ,30 ^{***} ,32 ^{***} ,33,34 ^{***} ,36,38]
Serum cytokine and procoagulant levels		
Elevated	21	[28 ^{***} ,29 ^{***}]
Normal	0	
Duration of hospital illness to death (days)		
0–1	5	[31 ^{***} ,32 ^{***} ,33]
1–10	18	[29 ^{***} –31 ^{***} ,33]
>10	14	[30 ^{***} ,31 ^{***} ,33,36]
Place of death		
Hospital	86	[28 ^{***} –32 ^{***} ,33,34 ^{***} ,36]
Nursing Home	6	[34 ^{***}]
Home	5	[34 ^{***}]
Cause of death		
Massive intracranial hemorrhage	3	[30 ^{***} ,32 ^{***}]
Pulmonary embolism	2	[30 ^{***} ,33]
Cardiopulmonary failure	50	[30 ^{***} ,33,34 ^{***} ,36]
Multisystem organ failure	6	[29 ^{***} ,34 ^{***} ,38]
SARS-CoV-2 RNA reactivity in brain sections		
Positive	24	[34 ^{***} ,35 ^{***} ,38]
Negative	61	[28 ^{***} ,31 ^{***} ,34 ^{***} ,36,38]
Neuropathology		
Acute microscopic ischemic infarcts	10	[28 ^{***} ,34 ^{***}]
Acute microscopic hemorrhagic infarcts	3	[28 ^{***} ,29 ^{***} ,35 ^{***}]
Petechial hemorrhage	3	[30 ^{***}]
Focal perivascular parenchymal T-cell infiltrates	8	[28 ^{***} ,29 ^{***} ,32 ^{***} ,35 ^{***}]
Diffuse perivascular parenchymal T-cell infiltrates	2	[29 ^{***} ,32 ^{***}]
Leptomeningeal inflammation	41	[30 ^{***} ,31 ^{***} ,34 ^{***}]
Interstitial brainstem inflammation	10	[30 ^{***} ,34 ^{***}]
Capillary endothelium expression of ACE2 receptor	1	[29 ^{***}]
Microglial nodules	1	[32 ^{***}]
Hypoxic ischemia changes and neuronal loss	27	[28 ^{***} ,31 ^{***} ,32 ^{***} ,33,36]
No abnormalities	3	[36,37]
Associated findings:		
Chronic infarction	8	[31 ^{***} ,34 ^{***}]
Alzheimer disease	5	[30 ^{***} ,31 ^{***}]
Lewy body disease	3	[31 ^{***} ,36]
Primary brain tumor	1	[31 ^{***}]
Multiple sclerosis	1	[36]
Metastatic cancer	1	[34 ^{***}]

due to a dysregulated, postinfectious autoimmunity response, analogous to the cytokine storm of severe viral influenza illness [53]. Recognizing the importance of a given patient's immune response to the SARS-CoV-2 exposure, patients have been recruited to participate in studies to examine B-cell and T-cell repertoire and immune responses during the acute and resolved phases of Covid-19 infection at home and in the hospital (ClinicalTrials.gov Identifier: NCT04362865). Four immunotherapeutic approaches are being used to stem the Covid-19 pandemic by targeting the immune system, in keeping with the multiplier effect of infection, immunity, and inflammation known as I-Cubed (I^3) [54]. The oral antimalarial drug hydroxychloroquine was the first highly publicized agent recognized for its immune-mediated mechanisms of chemotaxis, phagocytosis and superoxide production by neutrophils to inhibit SARS *in vitro*. It was administered in an open-label nonrandomized clinical trial of 20 adults and minors with severe Covid-19 illness with improvement, and later made widely available as prophylaxis [55]. An observational study of 1446 hospitalized adult patients at a New York City hospital with Covid-19 illness did not show a significant association between hydroxychloroquine use and intubation or death (hazard ratio, 1.04, 95% CI, 0.82–1.32), with similar findings in multiple sensitivity analyses [56].

The biological agent remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases is showing the greatest promise in reducing fatality due to its *in vitro* activity against SARS-CoV-2 by inhibiting the activity of RNA-dependent RNA polymerase [57]. A clinical protocol allowing expanded access to remdesivir (ClinicalTrials.gov Identifier: NCT04323761), and several clinical studies have begun recruiting subjects in an randomized, open-label, controlled clinical trials, in collaboration with the WHO (ClinicalTrials.gov Identifier: NCT04330690). A phase III randomized study comparing the safety and efficacy and antiviral activity of two remdesivir regimens with respect to clinical status is recruiting subjects (ClinicalTrials.gov Identifier: NCT04292899).

Convalescent plasma transfusion of SARS-CoV-2-specific IgG and neutralizing antibodies have been administered in uncontrolled case series to critically ill adult patients with Covid-19 with clinical improvement [58]. These preliminary findings suggest a role for transfusion therapy in the treatment of critically ill patients with Covid-19. A pilot prospective study collecting plasma to measure neutralizing antibodies to SARS-CoV-2 in recovered subjects is recruiting subjects (ClinicalTrials.gov Identifier: NCT04344977).

Treatment with 2 g/kg high-dose intravenous immune globulin (IVIg) therapy administered to three adult patients over 4–5 consecutive days in the early stages of clinically apparent SARS-CoV-2 viremia, alone (one patient) or in association with antiviral and antibacterial antibiotics showed clinical stabilization and were uneventfully discharged from the hospital [59]. Early administration of IVIg is first-line therapy in children with KD that appears to be missed or delayed during the Covid-19 pandemic etiologically related to SARS-CoV-2 infection prompted a single-center, randomized, open-label, controlled study in Peking China to evaluate the safety of IVIg in conjunction with standard care for severe 2019-nCoV pneumonia has not started recruiting subjects (ClinicalTrials.gov identifier NCT04261426). However, no similarly available studies have been announced in the United States.

An anecdotal prospective analysis of 55 children and adults treated with maintenance (400 mg/kg monthly) and high-dose (2 g/kg) IVIg therapy to treat diverse acquired and postinfectious autoimmune neurological disorders, found no new cases of SARS-CoV-2 stratified by a single home infusion service via phone interviews at the height of the Covid-19 pandemic (when it would have been impermissible for a nurse to enter the home) [60^{***}]. This uncontrolled observation suggests that Ig therapy delivered via intravenous, subcutaneous, or intramuscular routes may yet have an important role in Covid-19 illness prevention among vulnerable individuals. However, a longer period of follow-up of this cohort will be necessary to confirm these observations, as are further controlled studies to identify the dose and frequency of IVIg treatment to confer prophylactic efficacy.

Efforts to develop a safe and efficacious 2019-nCoV vaccine were underway in early 2020. Whole, live-attenuated or inactive whole virus vaccines represent a classic strategy for viral vaccinations similar to the Ebola vaccine platform employing an adenoviral vector. However, live virus vaccines often require extensive additional testing to confirm their safety. This is especially an issue for coronavirus vaccines, given the findings of increased infectivity following immunization with live or killed whole virus SARS coronavirus vaccines. Subunit vaccines for both SARS coronaviruses rely on eliciting an immune response against the spike protein to prevent its docking with the host ACE2 receptor. There are also advanced nucleic acid vaccine platforms for Covid-19. More recently, new modifications and formulations have improved nucleic acid performance in humans, with an expectation that this approach might eventually lead to the first licensed

human nucleic acid vaccine. There are now at least half-dozen candidates, including live viruses, recombinant protein subunits, and nucleic acids that may ultimately offer promise as preventive vaccines. However, each require additional manufacturing steps and formal toxicology testing before submitting a regulatory package to national regulatory agencies to be able to commence the clinical development, proceeding through first with phase 1 clinical trials for safety and immunogenicity, and later, phase 2 and phase 3 trials for both safety and efficacy [61]. However, the induction of protective immunity comes with a possibility of adverse effects. A preponderant emergence of post-vaccination vasculitis [62[¶]] led to formal guidelines for case definition [63].

CONCLUSION

Given their high prevalence and wide distribution, prominent genetic diversity, genomic recombination, and human–animal interface activities in certain parts of the world, the Covid-19 pandemic and other novel coronaviruses will likely continue to proliferate [64]. This depends upon multiple factors not the least of which is superspreading that occurs when single patients infect a disproportionate number of contacts across continents enhanced by travel [65]. With them comes the foreseeable risk of rising fatality and expected neurological complications. Adults with SARS-CoV-1 and the CoV-2 show inflammatory vasculopathy, encephalitis, and silent infarctions at postmortem examination, with variable SARS-CoV-2 RNA genomes by PCR. Children with MIC are purported to have a clinical syndrome that may resemble KD, however histopathology in life or at postmortem has not been documented in these cases. This has led to innovative treatments aimed at viral eradication and immunotherapy directed at heightened postinfectious inflammatory response termed I-cubed that expresses the multiplier effect of infection, immunity and inflammation in the context of genetics and other environmental exposures.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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