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Sex differences in neurologic presentation and outcome of SARS-CoV-2, especially cerebrovascular manifestations

Abstract

Neurological manifestations of COVID-19 and their impact have not been well characterized. Neurological involvement may be caused directly by the effects of the virus infecting the brain or indirectly by the local and systemic immune responses against the virus. Acute cerebrovascular disease, particularly ischemic stroke, has emerged as a serious complication of infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The arrival of COVID-19 represented a unique occasion to study sex difference, and accentuated the need for further study to elucidate the mechanisms that differentiate clinical outcomes among male and female patients. Recent pandemics has a clear sex disparity in clinical outcomes, and morbidity and mortality from COVID-19 are higher among men. Interestingly, the previous decade, there was sparse literature evaluating the impact of sex differences on outcomes in infectious diseases, especially on neurologic complications. Ongoing advances in scientific research have demonstrated sex differences in the neurological complications of neuroinfectious diseases, and sex and disparities in health care are frequently encountered. The evidence for potential sex differences and gender inequalities, including socioeconomic status and occupational exposure in the COVID-19 pandemic is continuing to emerge. In summary, sex is increasingly recognized as a critical determinant of health and disease, particularly relevant to the topical COVID-19 pandemic. Morbidity and mortality from COVID-19 are greater for males, however, the mechanisms for this difference are unclear. Understanding the differences in outcomes between males and females improve the effectiveness of health interventions. However, outcomes of the neurologic complications of infectious disease may be partially explained by sex differences in immune responses. With this narrative, we intend to provide the reader with a comprehensive coverage of where we currently stand regarding sex differences specific, especially on outcomes critical neurologic manifestations of the SARS-CoV-2 infection.

Keywords: COVID-19, inflammation, neurological complication, sex differences, immune system, neurologic prognosis

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Introduction

So far, no systemic viral infection in the world has had a higher social impact than SARS-CoV-2. The worldwide SARS-CoV-2 pandemic was responsible for millions of deaths and caused the third zoonotic disease of a tremendously pathogenic coronavirus. The disease SARS-CoV-2 causes is called coronavirus disease 2019 COVID-19. SARS-CoV-2, a much more contagious virus than SARS-Covid 1, was first reported in December 2019 and emerged in Wuhan, (Hubei province, China), rapidly evolving into a pandemic and endangered human life. Current evidence suggests that the virus spreads mainly between people typically transmitted through infected respiratory fluids, when an infected person coughs, sneezes, or talks (within 1 m). In most cases, symptoms appeared up in the newly infected person about 5-6 days after contact. Notwithstanding, increasing international efforts, COVID-19 remains one of the most infectious diseases, with changing viral variants with new strains and strategic immune evasion,[1] as the pandemic continues, there will be more variants. Based on the clinical investigations, people with COVID- 19 infection can may be asymptomatic or result in moderate to fatal.[2] COVID-19 mostly manifests as pneumonia, involving the lower respiratory tract. The most reported initial symptoms in descending order include dyspnea (30.64%), cough (54.21%), fever (57.93%), and neurological symptoms (20.82%)[3] However, signs and symptoms of COVID-19 are many and various in the whole population. Evidence about the involvement of other organs is increasing including brain, kidneys, gastrointestinal tract, and heart can be affected by this virus, through direct, indirect, post-infection damage. Outcomes of COVID-19 vary between men and women. Male sex, advanced age (>65 years) type 2 diabetes, and cardiovascular disease are at raise risks serious natural history and poor prognosis of COVID-19.[4] Considering this difference in the impact on health of SARS-CoV-2 infection between men and women, different approaches have been proposed provide an explanation of this disproportionally impacted males. However, the exact mechanisms of these differences are not completely understood. Although the virus is intended a respiratory pathogen, multitude neurologic manifestations manifest during COVID-19, complex scenarios can occur. Neurological symptoms of COVID-19 infection events have been documented since the first case series originating out of Wuhan, China. SARS-CoV-2 infection is known to affect the central nervous system, peripheral nervous and musculoskeletal system,[5] and evidence of its neurological involvement is mounting. Potential complications have been found at different stages of infection, both during the acute and chronic stages of infection.[6] Additionally, the start of symptoms can help differentiate acute from post-infective complications. Several neurologic complications have been described, both as parainfectious/acute neurological and postinfectious phenomena.[7] Recent evidence indicates that gender disparities are implicated in clinical outcomes of SARS-CoV-2 infection, with men being more likely to have higher disease severity and mortality than women.[8,9] Differences in women's

and men's bodies due to their sex is playing a role in people's risk of illness and death due to novel coronavirus. A report from the Italian National Institute of Health,[10] data retrieved from the Italian National Surveillance System of COVID-19 confirmed infections, demonstrate similar numbers of cases in women and men, but proportion of deaths due to COVID-19 was major in men (56.46%) compared to women (43.54%). Most of the observed deaths manifested in the elderly. Increase in number of data reported in the literature, have made particularly evident the need for further study for explain the underlying pathways that differentiate clinical manifestation among women and men, especially on neurologic complications. The task of the Global Health 50/50, an autonomy research initiative, is monitoring differences in SARS-CoV-2 infection, illness and death among women and men,[11] and the database tracked data disaggregated by sex showing fewer deaths attributable to SARS-Covid 2 infection (43% vs 57%) for women. This tracker presents the sex-disaggregated data being reported by governments. Research of sex differences in neurological symptoms was emphasized from the early months of the extraordinary pandemic, and SARS-CoV-2 infection has a clear sex disparity in clinical outcomes. Clinical manifestation shows that males suffer both a higher severity and fatality for SARS-CoV-2 infection than females.[12] It has been presumed that non-biological aspects of being a man or a woman as gender (role in the work, gender-linked health behaviors, occupational exposures, relations, and institutionalized gender and norms for men and women) may influence SARS-CoV-2 infection and could provide a better understanding for the observed sex divergence in infections outcome between male and female patients.[13] The literature is still being updated very fast, as new studies are published every day. More specifically, in this narrative review, we discuss our current main knowledge about sex differences, especially in its neurological forms and infectious disease outcomes of SARS-CoV-2, presenting circumstances with more recent findings.

Neurological involvement in novel coronavirus

SARS-CoV-2 is endemic, and most common body system affected is the pulmonary causing acute and sometimes severe pulmonary symptoms and hypoxia. Pulmonary manifestations include shortness of breath, cough, sputum production, respiratory failure, and acute respiratory distress syndrome (ARDS). However, SARS-CoV-2 infection is not merely a respiratory disease, and the pandemic has shown that this virus can affect the entire body, including the nervous system. There is a wide diversity of neurologic manifestations, some of them severe, in the *range* of COVID-19 disease. Recent literature highlights what is currently known about the effects of COVID-19 on the nervous system, the importance of increased research into the underlying causes and possible ways to treat its symptoms. Neurological symptoms may appear, both during the acute phase and in the post-acute phase of the infection. In early clinical study conducted in China**,** a clinical series of hospitalized patients from Wuhan > 45% of COVID-19 patients had neurological symptoms that involved both the central nervous system and the peripheral nervous system, stroke, altered mental status, anosmia/ageusia, and seizure, muscle/nerve disease.[14] Neurological complications have been described as well: stroke, encephalitis, myelitis, seizures, dizziness, headache, anosmia, ageusia, and myalgia.[15] Severe neurological complications following COVID-19 infection, including cerebrovascular disease (ischemic stroke, hemorrhagic stroke, cerebral venous thrombosis, posterior reversible encephalopathy syndrome), encephalitis, encephalopathy, headache, brain fog, long covid, polyneuropathy, myopathy, neuromuscular disease, depression, seizure, sleep disorders, and anxiety.[16] Of the better described, the most relevant neurological manifestations connected with COVID-19 have been anosmia, encephalopathy, and stroke.[17] According to the systematic review, the prevalent neurological manifestations were Guillain-Barré syndrome (GBS) and its variants (24%), succeed by encephalopathy (21%).[18] Stroke is one of the most fearsome neurological complications caused by SARS-CoV-2 infections has its own unique clinical features. Among the most reported cerebrovascular diseases are ischemic stroke, hemorrhagic stroke, cerebral vasculitis, and cerebral venous thrombosis.[19,20] Among 18,258 COVID-19 patients, 2791 they exhibited neurological symptoms, which were classified into different types. The prevalence of cerebral ischemia was 2.9% and that of cerebral thrombosis was 2.2%.[21] A retrospective cohort study of 236,379 patients with COVID-19, whereas the incidence of ischemic stroke was 2.10 percent.[22] Out of a total of 388 patients (mean age 66 years, 68% men, 16% requiring intensive care, found that 2.3 percent of patients had an ischemic stroke.[23] COVID-19 associated hemorrhagic stroke is less *common* than ischemic stroke. A meta-analysis of 108,571 patients, the most prevalent manifestation was acute ischemic stroke (87.4%); intracerebral hemorrhage was less frequent (11.6%).[24] A retrospective cohort study found that 35 of 5227 (0.67 percent) COVID-19 patients contracted subdural hemorrhage, subarachnoid hemorrhage, or intracerebral hemorrhage.[25] Although an underestimation cannot be excluded, prevalence estimation from pooled samples of patients with COVID-19 of acute cerebrovascular disease was 2.3%, of which majority were ischaemic stroke 2.1%, followed by haemorrhagic stroke 0.4%, and cerebral venous thrombosis 0.3%.[26] COVID-9 is related with encephalopathy and delirium. The prevalence of encephalopathy associated with COVID-19 is very different in the various research on the topic, alternating from 7 to 69%.[27] Encephalitis is an uncommon but serious inflammatory condition of the brain that has been described as a serious manifestation of COVID-19, which is primarily caused by the autoimmune process and/or the viral infection[28] and considered a medical emergency requiring urgent care. The pooled mortality rate from COVID-19-associated encephalitis is described to be 13.4%, and normally occurred 14.5 days after the diagnosis of SARS-CoV-2 infection.[29] Inflammatory of the brain is described in less frequency of 0.22% than encephalopathy, which appeared at a rate of 8.7% amongst 12,601 hospitalized COVID-19 patients and affected patients with severe COVID-19 infection *above all others.*[30] According to a prospective study of the first 100 consecutive patients brain fog was the most relevant persistent neurologic manifestation in those spared from the virus (81%) without history of serious disorder or breathing problems.[31] Headache is an important symptom present in COVID-19 infection, which is observed in about one quarter of symptomatic individuals.[32] Guillain-Barre syndrome (GBS) is a rare condition in which a person's immune system affects the peripheral nervous system, usually preceded by infection. GBS relates to numerous infections, and Covid-19 patients with GBS can present with diversified symptoms. However, GBS is a rare, heterogeneous disease. Although a rarely occurring disease, a few descriptions point towards what appears to be on the rise incidence in 2020, which coincides with the peak of the novel coronavirus outbreak.[33] A retrospective multicenter study in Italy, it was found that the incidence of GBS elevated by 2.6 times during pandemic waves of March–April 2020 in comparison to the period of time of March–April 2019, where 88% of GBS cases were diagnosed as positive for Covid-19. Subsequent one of the first confirmed occurrence of GBS-associated SARS-CoV-2 infection reported in 2020, and numerous cases have been published during the COVID-19 pandemic.[34] Electroencephalographic (EEG) of patients with COVID-19 symptoms. revealed electroencephalographic abnormalities. Epileptiform changes, slowing of background activity (both generalized and focal), and periodic discharges were among the most frequently reported EEG changes.[35]

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Sex differences to neurologic complications of COVID-19

Critical manifestations like stroke

Strokes have an in-hospital mortality rate of 5% to 10% for ischemic stroke and 40% to 60% for intracerebral hemorrhage.[36] Acute stroke has been reported to be a rare disease in patients with COVID-19, with an incidence of 1%-6%.[37] Studies have revealed greater morbidity and mortality among patients with SARS-CoV-2 infection and stroke than among those with stroke alone.[38] For cerebrovascular disease, most manifestations arise within 21 days of COVID-19 onset, and stroke was rarely the first manifestation.[38] However, acute ischemic stroke is a complication of patients with grave COVID-19 infection attributable to hypercoagulable state.[39] Sex differences in COVID-19 infection, especially critical disease such as brain attack, have been highlighted. Global stroke statistics show significant sex disparities in stroke.[40] As stated by to the statistics, the incidence of ischemic stroke is more frequently than you think among men, whereas the rate of mortality associated with it is higher among women.[41,42] An observational study of patients with acute stroke and SARS-CoV-2 infection, found that severe in-hospital complications and worse outcomes after ischemic strokes were higher in males, than females. The study based in Chicago, included 83 patients with acute stroke, women had better outcomes: lower mortality (13% vs 38%, P 5.02), lower modified Rankin scale at discharge (OR 0.53, 95% CI 5 1.03–2.09), and were more likely to be discharged home (33% vs 12%, P 5 .04) when adjusting for age, race, ethnicity, and vascular risk factors.[43] Among these 83 patients 32 patients (39%) presented with stroke as the primary diagnosis, ischemic stroke was found to be often the subtype (77%), intracranial hemorrhage (19%) was second, followed by subarachnoid hemorrhage (4%). A retrospective cohort study one of the largest studies on stroke and COVID-19 included 387,330 COVID-19 patients' men. In this study, men had a 32% higher risk of stroke compared to women.[44] Authors[45] evaluated gender disparity in mortality between patients with stroke related to SARS-CoV-2 infection. The authors utilizing pooled deidentified data from 30 healthcare organizations, find COVID-19 patients via ICD-10 diagnosis or documented laboratory confirmation of SARS-CoV-2 RNA or antibodies. Betwixt 149,410 Covid-19 patients, 1,618 (1.1%) had a stroke diagnosis ± 30-days of verified Covid-19. Of the 1,609 patients (847 males and 762 females) were incorporated in primary analyses. Females were older (67.7 vs. 65.7 years) and were more likely to be of black race (34.1% vs. 27.6%). Therefore, in a tendency score matched sample of 634 men and 634 women, balanced by covariates, mortality was lower in women (11.7% vs 15.8% *P*=.04). Considering that male subjects are more likely to experience · intense infection SARS-CoV-2 symptoms requiring intensive care unit admission, it is not extraordinary that most of the patients developing stroke during COVID-19 are male (62 %), with a median age of 63 years.[46]

Additional neurological manifestations in the COVID-19 era

Since the first reports ageusia and anosmia have become a frequent clinical feature in Covid-19 infection.[47] The rate of identifying anosmia is 5.1%, ageusia is 5.6%, and chemosensory deficits is present at 19.4%.[48] A European study[49] including 417 mild-to-moderate COVID-19 patients concluded the study (263 females), 85.6% and 88.0% of patients showed that common symptoms were olfactory and gustatory dysfunctions, respectively. Women were affected relevant more by their hyposmia or anosmia ($p < 0.001$) or gustatory dysfunction (P=0.001). One of the more frequent and serious symptoms of Long COVID is Brain Fog. This neuropsychiatric symptom is clearly detailed as an altered state of consciousness in which a person is less wakeful, aware, alert, and focused than usual.[50] Brain Fog persisted as long as 5 months and females were much more likely than males (2.3:1) to exhibit "long hauler COVID-19" symptom.[51] It has been seen in a meta-analysis of 35 studies for 28,348 survivors that the prevalence of Long COVID-related headaches, adult age (52 years) and female sex have been found more frequently in patients with persistent headache at 9 months.[52] Previous investigations reported that female patients are more susceptible to long-term COVID.[53] Effectively females have been described to experience Long-COVID more likely than males. Understanding the evolution of neurological and neuropsychiatric symptoms of long COVID is decisive for accurate prognostic impact**.** Indeed, Long COVID symptoms as well as physical, cognitive, neurological, and neuropsychiatric appears to be more common in females than in males.[54] In general, men are at greater risk of contracting the COVID-19 disease severely or fatally. This can be attributed to the sum of the protective results of X-linked immune response genes and the female sex steroid hormones enhancing antibody production and mitigating innate immune inflammatory responses.[55]

Conclusion

Research on the topic is constantly evolving, so further studies on sex-disaggregated and gender-specific data are needed. However, our comprehension of the basic process sex differences in neurologic manifestations in COVID-19 outcomes is developing. It is currently not feasible to draw definitive conclusions about sex disparity prognosis in neurologic presentation in the COVID 19. More studies are essential to assess the extent to which COVID-19 differentially impacts the sexes in both the acute and post-acute phases. This may be beneficial for improve the effectiveness of health interventions and treatment interventions tailored to each sex. Further studies are required to deep understanding sex differences in the immune response in COVID-19. Regarding vaccines, in early 2021 due to the critical situation, the first vaccines were introduced, but COVID-19 vaccines are promptly approved for mass vaccination after leaving phase 3 of clinical studies. COVID-19 vaccines have been issued the emergency use authorization for current public health emergency and some of their potential subsequence side effects have been left out, especially on nervous system. Although vaccines are now considered the perfect way it is necessary to consider gender and gender in COVID-19 vaccine research, development, and delivery. Better comprehension may help to guide antiviral treatment and vaccinations. In doing so, better grasp of how sex influences COVID-19 outcomes in neurological symptoms will have impactful impact for the ongoing pandemic's clinical care and strategic guidance.

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Conflicts of interest

The authors have no conflict of interest.

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