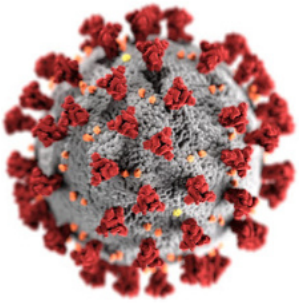

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
James Luby, M.D., and Robert Haley, M.D., editors

The Situation: U.S. Cases Approach 4.5 Million

In the world as of July 31, 2020, 17,322,041 cases of Covid-19 and 673,833 deaths have been confirmed. In the United States, there have been 4,495,224 cases, the most in the world followed in order by Brazil, India, Russia and South Africa. China is now 27th in the world with 87,610 cases. Deaths in the U.S. through July 31 have been estimated at 152,075.[1]

From March 10 through July 31, there have been 48,732 confirmed cases of Covid-19 reported from Dallas County with 609 deaths, about 30% of these from long-term facilities.[2] Of hospitalized cases in Dallas County, more than two-thirds have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men than women have died. Sixty percent of the cases have occurred in the Hispanic population. As of 7/21, 530 deaths have been analyzed by race with 27% occurring in Whites (actual White population 29%), Hispanics 44% (population 41%), Blacks 24% (population 24%), Asians 4% (population 7%). Specimens submitted for diagnosis of respiratory viruses show continuing positivity for SARS-CoV-2 with the latest result on 7/24 being 26.8%.

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 7/31/20)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 7/31/20

Feature Article

Neurologic Considerations of SARS-CoV-2 Infection

Anik Amin, MD and Kyle Blackburn, MD, Department of Neurology

As our experience with Covid-19 continues to grow, we are learning more about its impacts beyond the respiratory system. While serious neurological complications are rare, there are an increasing number of reports on the neurological manifestations of Covid-19. Traditional media outlets rapidly report on these as well. Involvement spans the neuraxis from brain to muscle. The mechanism behind each particular neurological complication is uncertain, but Covid-19 seems to affect the nervous system in three broad ways:

1) Neurological complications of systemic disease (perhaps most common)
2) Direct neuroinvasion of SARS-CoV-2. Definite cases are exceedingly rare, despite ACE2 receptors in nervous system tissue and associated vessels.
3) Para-infectious or post-infectious immune mediated responses

Mild Neurological Symptoms

Myalgia, headache, and "brain fog" are relatively common in Covid-19 patients. A peculiar, common symptom is loss of taste and smell, often without coryza. In a European study of 417 patients infected with SARS-CoV-2, 86% reported abnormal smell, and 82% reported abnormal taste.[1] Mechanisms for anosmia remain unclear, though a recent report of anosmia associated with imaging changes in the gyrus rectus suggests some cases may be central in origin.

Encephalopathy and Encephalitis

Encephalopathy is one of the more common neurologic symptoms of Covid-19, and can involve delirium and psychiatric features. In most instances, encephalopathy is likely the result of metabolic derangements and impaired homeostatic functions accompanying critical illness. However, reports of patients with evidence of neuroinflammation suggest that SARS-CoV-2 can be associated with an encephalitis. While viral replication in the CSF was confirmed in one case, the majority of reported encephalitis cases have only demonstrated evidence of infection in nasopharyngeal samples.[2] A case of autoimmune encephalitis with NMDA antibodies suggests that some cases of Covid-19-associated encephalitis may be immune-mediated. A case of acute necrotizing encephalopathy with hemorrhage affecting bilateral thalami and other midline structures has also been reported.[3]

Acute Disseminated Encephalomyelitis

Immune-mediated neurologic disorders associated with Covid-19 are increasingly reported in the literature, though rigorous epidemiologic study is needed to confirm an increased prevalence. Cases of acute disseminated encephalomyelitis (ADEM), a polyfocal demyelinating disorder, have been reported. While ADEM is classically considered a pediatric disorder, all reported cases to date have occurred in adults. A case resembling ADEM in a patient with severe Covid-19 was recently recognized at our center. A case of idiopathic transverse myelitis responsive to immunotherapy has also been reported.[2]

Peripheral Nervous System

Cases of parainfectious Guillain-Barre syndrome (GBS) are frequently reported in the neurologic literature, although current evidence does not support an increased incidence compared to other respiratory infections. It is speculated that GBS cases result from molecular mimicry due to significant homology between the spike protein on SARS-CoV-2 and peripheral nerve gangliosides.[4] Covid-19-associated GBS may present as the "classic" demyelinating radiculoneuropathy, but other phenotypes, including acute motor axonal neuropathy (AMAN) and Miller Fisher syndrome, have also been reported. Muscle injuries associated with CK elevations and rhabdomyolysis are likely secondary to the burden of critical illness.

Stroke

The evidence for an association between Covid-19 and major vascular events is growing. It seems that Covid-19, particularly when severe, induces a hypercoagulable state. Postulated mechanisms include activation of inflammatory and thrombotic pathways and/or viral damage to endothelial cells expressing ACE2 receptors. Early studies out of Wuhan, China, and Italy reported cerebrovascular manifestations in 2-6% of hospitalized Covid-19 patients.[2] Most patients are older and have vascular risk factors, but serious cases have occurred in younger patients. One hospital in New York reported five cases over two weeks of large vessel occlusion (LVO) strokes in patients younger than 50 years, over six times the expected frequency. Two patients had no prior vascular risk factos.[5] At our centers we have seen one known case of LVO in a Covid-19 patient under 50 years of age. She also had severe mitral valve disease. Well-designed case control studies will better elucidate the relationship between Covid-19 and stroke.

Conclusions

SARS-CoV-2 infection has been associated with a myriad of neurologic sequelae that are hypothesized to occur via diverse pathophysiologic mechanisms. Overall, the proportion of Covid-19 cases with major neurological symptoms is low. The current evidence suggests that the virus has neurotropic potential and may trigger autoimmunity and other complications in susceptible individuals. An important issue is whether SARS-CoV-2 infection is sometimes just coincidentally associated with certain neurological symptoms. This becomes more likely as prevalence in the community increases and patients present with neurological symptoms without significant respiratory symptoms.

Neurological complications like ADEM and stroke cause long-term disability and impact prognosis. Even if the proportion of Covid-19 cases with significant neurological complications is low, the absolute number of cases as prevalence grows could reach a point of significant socioeconomic burden. Further study is needed to elucidate the associations between Covid-19 and neurological symptoms as well as to determine the long-term sequelae of Covid-19 on the nervous system.

References:

1. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of COVID-19: a multicenter European study. *Eur Arch Otorhinolaryngol* 2020; 2020/04/06. DOI: 10.1007/s00405-020-05965-1.
2. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020 2020/07/06. DOI: 10.1016/S1474-4422(20)30221-0.
3. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020. 2020/03/31. DOI10.1148/radiol.2020201187.
4. Dalakas MC. Guillain-Barre syndrome: The first documented COVID-19-triggered autoimmune neurologic disease: More to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm* 2020; 7 2020/06/11. DOI: 10.1212/NXI.0000000000000781.
5. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med*. 2020;382(20):e60. doi:10.1056/NEJMc2009787

News Update

Negative Clinical Trial Results

Sarilimumab, an IL6 receptor antagonist, failed to reach its primary and secondary end-points in a trial evaluating the drug in patients with pneumonia due to Covid-19. Tocilizumab, another IL6 receptor antagonist, did not reach its primary and key secondary end-points in patients with Covid-19 pneumonia. There was no benefit in a trial with this medication with regard to mortality and ventilator requirements. The drug continues to be studied in other randomized controlled trials.

From the Editors

The editors thank Drs. Amin and Blackburn for their feature article on neurological complications of Covid-19.

The aim of this weekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (COVID-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.