

COVID-19 Action Newsletter

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The Situation: Confirmed U.S. Deaths Pass 315,000

In the world as of December 21, 2020, 76,975,940 cases and 1,695,846 deaths have been confirmed. In the United States, there have been 17,860,634 cases, the most in the world followed in order by India, Brazil, Russia and France. China is now 78th in the world with 95,135 cases. Deaths in the U.S. through December 21 have been estimated at 317,729.¹

From March 10 through December 11, there have been 141,303 confirmed cases of Covid-19 reported from Dallas County with 1,315 deaths, about 22% of these from long-term care facilities.² Sixty-eight percent of hospitalized cases in Dallas County have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men (63%) than women (37%) have died, and 47% of the hospitalized cases have occurred in the Hispanic population. As of 12/11, deaths have been analyzed by race with 25% occurring in Whites (actual White population 29%), Hispanics 46% (population 41%), Blacks 25% (population 24%), and Asians 3% (population 7%). Specimens submitted for diagnosis of respiratory viruses show continuing positivity for SARS-CoV-2 with the latest result on 12/55 being 21.6%, down from a peak value of 30.5% obtained during the week ending 7/4/20. Influenza A and B antigen tests and RSV antigen tests in specimens from the respiratory tract from 10/3 through 12/5/20 have been negative.

References:

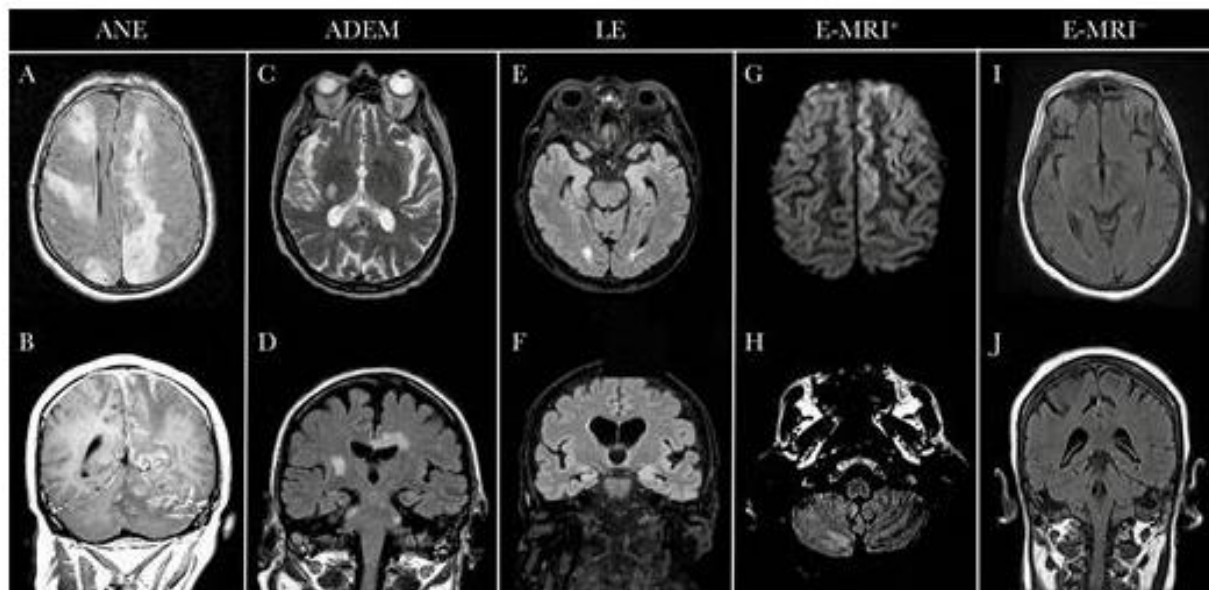
1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 12/21/20)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 12/5/20

Clinical Update

Encephalitis in Covid-19. The ENCOVID Multicenter Study from Northern Italy

Drs. Anik Amin and Kyle Blackburn of UT Southwestern's Department of Neurology and Neurotherapeutics summarized the status of CNS disease in Covid-19 in a prior newsletter (*C.A.N.* 7/31/2020). A recently published article has updated their review with an analysis of 25 cases of encephalitis occurring in the course of the Covid-19 epidemic in Northern Italy between Feb. 20 and May 31, 2020.¹ This region was intensively involved during this period with 13 centers caring for 43,139 cases of laboratory-documented Covid-19. The study population excluded patients with acute cerebrovascular disease to accumulate the 25 patients reported. To calculate incidence statistics, they also excluded 1 patient with acute disseminated encephalomyelitis (ADEM) and two patients with acute necrotizing encephalitis (ANE). During the study period, they studied 22 patients with encephalitis out of a total of 43,139 patients with documented Covid-19 disease. This translates to an estimated 50 cases of encephalitis per 100,000 Covid-19 cases. Their report summarizes the data on the larger group of 25 patients and includes the one case of ADEM and the two with ANE.

Of the 25 patients, 2 had ANE, 1 had ADEM, 2 had limbic encephalitis (LE), 7 had clinical encephalitis with positive MRI findings (E-MRI+), and 13 had clinical encephalitis with negative MRI abnormalities (E-MRI-). Onset of CNS disease was concomitant with Covid-19 in 11 cases; in 12 cases, neurological disease followed Covid-19 (range 5-12 days). In two patients, CNS disease preceded Covid-19 by 3 and 5 days, respectively. The most common symptoms were altered mental status in 17, aphasia and/or dysarthria in 6, and seizures in 6. Headache was present in 10 patients during the course of illness. EEG was abnormal in all the patients. CSF was abnormal in 17 patients, 15 of whom had elevated protein levels (50-123 mg/dL), and 9 had pleocytosis (5-55 cells). Fourteen patients had RT-PCR determinations on CSF with the study being repeated in 5 patients, and all CSF tests for SARS-CoV-2 were negative. Brain MRI images were done in all and were abnormal in 12 patients (Figure 1).¹ ADEM was seen in 1, ANE in 2, LE in 2 and heterogeneous alterations in 7. Thirteen patients had normal MRI findings. Four of the 25 patients died. Response to high-dose methylprednisolone was thought to be positive in the ADEM patient, one patient with LE, and 3 of the patients with negative MRI findings; whereas, no response was seen in ANE or any of four patients with encephalitis with positive MRI findings.



Brain MRI findings according to encephalitis phenotype. A,B, Acute necrotizing encephalitis. C,D, Acute disseminated encephalomyelitis. E,F, limbic encephalitis. Note bilateral medial temporal lobe involvement. G,H, Encephalitis with MRI alterations (E-MRI+). I,J, Encephalitis with negative MRI (E-MRI-).

Encephalitis is usually thought of as being primarily infectious, due directly to a virus or another microbiological agent or post-infectious where the CNS injury is mediated by immune mechanisms.^{2,3} The authors of this article point out the similarity of encephalitis encountered in their patients to a post-infectious etiology. The 25 patients in the present study all had positive pharyngeal RT-PCR tests for SARS-CoV-2. Neurological manifestations in 12/25 occurred after a latent period of 5-12 days after illness onset. A latent period is usually not seen or is short in duration in primary infectious encephalitis. The patients usually had clinical neurological manifestations. All had abnormal EEGs, and the CSF was abnormal in 17. Fourteen of the 25 patients had CSF RT-PCR tests that were negative in contrast with a classical primary infectious encephalitis like herpes simplex encephalitis where the CSF is positive for virus in greater than 95%. They did not study the CSF for SARS-CoV-2 antibody; whereas, antibody titers to herpes simplex virus usually increase during the course of illness. No real statement can be made as to the efficacy of steroid therapy since only a few patients were studied.

References:

1. Pilotto S, Masciocchi S, Volonghi I et al. Clinical Presentation and Outcomes of Severe Acute Respiratory Syndrome Coronavirus 2-Related Encephalitis: The ENCOVID Multicenter Study. *J Infect Dis* 28 September 2020. DOI: 10.1093/infdis/jiaa609

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3. Haider A, Saggiqa A, Ali N, Dhallu M. Covid-19 and the Brain: Acute Encephalitis as a Clinical Manifestation. *Cureus* 2020; 12(10): e10784. DOI: 10.7759/cureus.10784

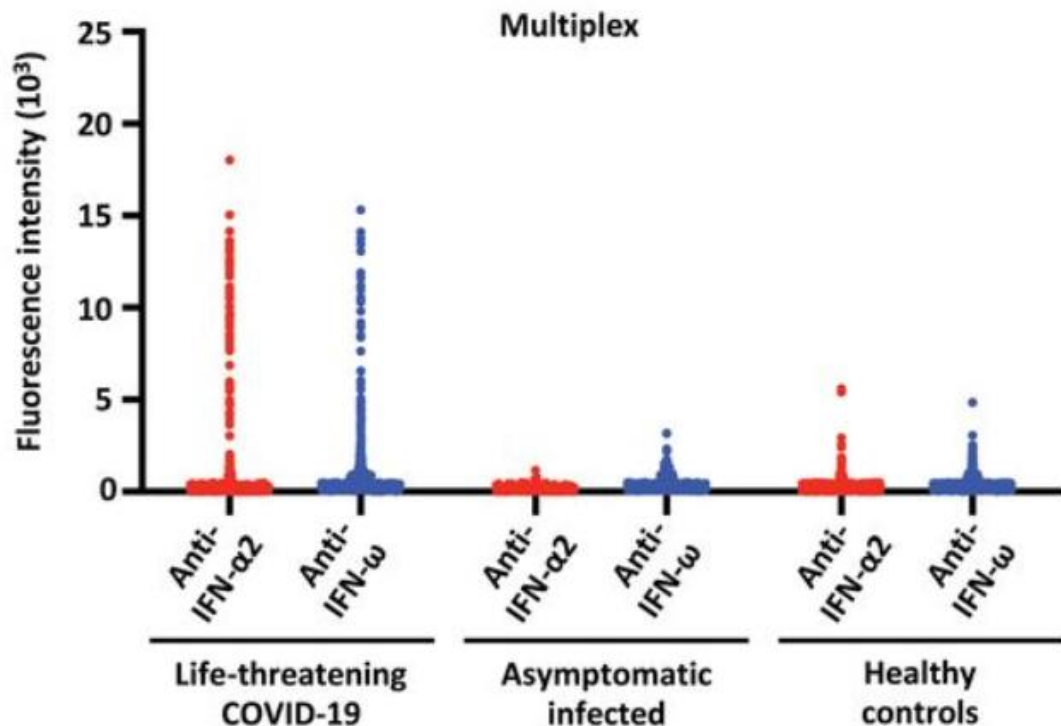
Clinical Advance

Auto-antibodies to Type 1 Interferons: Association with Severe Covid-19

Type 1 interferons (IFN) are a series of discrete proteins produced in humans that may have antiviral effects and play an important role in innate immunity. Auto-antibodies (auto-Abs) can be formed against these proteins and negate their positive effects. Patients with certain diseases like auto-immune polyendocrinopathy, type1 (APS-1) may have such antibodies; they were studied in 3 patients with severe Covid-19, found to be present, possibly influencing the course of disease. Almost all patients with APS-1 are known to have neutralizing antibodies of the IgG class to type 1-interferons. Based on these findings, the authors set upon studying auto-Abs to type 1 interferons in a larger set of patients with life-threatening Covid-19 as compared to those with asymptomatic or mild disease and uninfected patients. These patients from Northern Italy were studied during the most recent epidemic.

Auto-Abs to type 1 interferons were measured in serum during the acute phase of illness by the luciferase immunoprecipitation system (LIPS) and by ELISA. At least 101 of 987 patients (10.2%) with life-threatening Covid-19 pneumonia had IgG auto-Abs against type 1 interferons (interferon-omega and the 13 types of interferon-alpha); whereas, none of the 663 with asymptomatic or mild disease tested had such antibodies (0/663, 0%, Figure).

They were present in only 4 of 1,227 (0.33%) healthy patients before the pandemic. The differences between 10.2% vs 0% and 10.2% vs 0.33% were highly statistically significant. One-half of the auto-Abs-positive patients were over 65 years of age, and 94% of the 101 positive patients were men. Critical Covid-19 disease is known to predominate in the elderly and in men.



Neutralizing auto-Abs against type 1 interferons (IFN-α2 and IFN-omega) in patients with life-threatening Covid-19 and asymptomatic, mild infections and healthy controls

The authors cited the following lines of evidence supporting their thesis that auto-Abs against type 1 interferons precede Sars-CoV-2 infection and cause critical Covid-19:

- 1.) Two patients with positive auto-Abs tests and critical illness had sera stored and were found to have auto-Abs before infection.
- 2.) Three patients with APS-1 were positive for auto-Abs before infection and then developed critical Covid-19 when infected.
- 3.) Thirty-two women with incontinentia pigmenti were screened for auto-Abs against type 1 IFNs; 25% were positive including one who later developed critical Covid-19.
- 4.) The tendency for critical disease to develop in elderly men can be explained by the occurrence of auto-Abs in this population.

References:

1. Bastard P and Rosen RB: Autoantibodies against type 1 IFNs in patients with life-threatening Covid-19. *Science* 2020; 370: eabd4585. DOI: 10.1126/science.abd4585.
2. Lopez de Padilla CM, Niewold TB. The Type 1 Interferons: basic concepts and clinical relevance in Immune-mediated Inflammatory diseases. *Gene* 2016; 576(1 Pt 1): 14-21. DOI: 10.1016/j.gene.2015.09.058.
3. Beccuti G, Ghizzone L, Cambria V, et al. A Covid-19 pneumonia case report of autoimmune polyendocrine syndrome type 1 in Lombardy, Italy: letter to the editor. *J. Endocrinol Invest* 2020; 43: 1175-1177. DOI: 10/1007/s40618-020-01323-4.

From the Editors

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.