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Influenza associated acute necrotizing encephalopathy and COVID-19 encephalopathy; a comparative review

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Abstract
Acute necrotizing encephalopathy (ANE) is influenza-associated encephalopathy (IAE) that mostly occurs in younger age groups following an acute viral illness with a very low recovery rate. It is a rare but rapidly progressive neurodegenerative disorder which pathogenesis is still not clear. There are some cases reported where the virus can directly invade the central nervous system (CNS) through the peripheral nervous system. Several pathogenic conditions like rising levels of proinflammatory cytokines, dissolving the blood-brain barrier (BBB), etc can trigger the viral infection. There are no specific treatments available but initial steroid therapy in combination with antivirals and hypothermia therapy were found efficacious in some cases. Similarly, coronavirus disease 2019 (COVID-19) encephalopathy is caused by a novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2). Having a very low recovery rate, and still unknown pathophysiology, this condition is proved to be fatal for immunocompetent adults. Treatments are not available but drugs like remdesivir, hydroxychloroquine, tocilizumab, and losartan were used to reduce the viral infection. No recurrent cases have been reported so far, but reinfection of the virus can trigger hypoxic encephalopathy. This review mainly focuses on a comparative study to understand the pathophysiology to help for discovering a new area of drug development.
Keywords: Acute necrotizing encephalopathy, Influenza-associated encephalopathy, COVID-19 encephalopathy, Severe acute respiratory syndrome coronavirus-2
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Introduction

Influenza viruses are the common seasonal flu-causing viruses that belong to the family *Orthomyxoviridae*. Among them, influenza A and influenza B viruses are found to infect human populations preliminarily infecting the respiratory tract. Persons susceptible to these viral infections are immunocompetent adults, children and, older age groups. Spreading through droplet infection and contaminated surface or contact, influenza viruses are known to cause global pandemics, like the most recent occurred 2009 "Swine Flu". Around 3-5 million cases per year and 250 000-500 000 deaths are the results of influenza infection. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel coronavirus is responsible for the currently occurring pandemic of COVID-19 as declared by World Health Organization (WHO) in March 2020. According to a phylogenetic investigation, SARS-CoV-2 is closely related to the genera of beta coronaviruses under the family *Coronaviridae* (1). Coronavirus transmission occurs through droplet infection, but now there is enough proof that airborne and fecal-oral transmission can be possible. Though all age groups are equally susceptible to coronavirus infection, most individuals remain asymptomatic.

Encephalopathy is a condition that occurs due to an infection or disease which alters the nervous system structure or function. Acute necrotizing encephalopathy (ANE) can be associated with the human herpes virus-6 infection, measles, parainfluenza, *Mycoplasma* infection along with influenza. Severe complications of ANE are altered mental status, seizures, coma, and even death, however those who recover mostly show neurologic sequelae. Familial or recurrent ANE has also been reported due to mutations in the nuclear pore gene RANBP2, called ANE1 or infection induced acute encephalopathy-3 (IIAE3) (2).

Encephalopathy can be caused by SARS-CoV-2 or novel coronavirus disease 19 as well, but it has not been well distinguished. SARS-CoV-2 could directly invade the central nervous system (CNS) resulting in neurological change or could aggravate the pre-existing neurological complication or make one susceptible to neuronal

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Implication for health policy/practice/research/ medical education

Acute necrotizing encephalopathy (ANE), categorized under influenza-associated encephalopathy (IAE), is a relatively known neurological disorder than coronavirus disease 2019 (COVID-19) encephalopathy that caused by a novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2). Both virus showed similar mode of first neurological infection (through respiratory system) but the different pathological mechanism. The diagnosis, symptoms and treatment are also varying in both viral encephalopathy. This review provides a comparative study of infection mechanism, diagnosis, pathophysiology and treatment options, which will be helpful for discovery of new drugs and proper treatment of COVID-19 encephalopathy.

damage by other means (3). Different neurological symptoms of COVID-19 are altered consciousness, anosmia, paresthesia, ageusia, ischemic stroke, seizures, and cerebral hemorrhage. The most worrying fact about COVID-19 related nervous system complications is that they may not occur suddenly after a viral illness, but can have a long-term or permanent neurological dysfunction.

The purpose of this review is to establish a comparative account of study between influenza-associated ANE and COVID- 19 encephalopathy which will be able to help in understanding its diagnosis, pathophysiology, treatment and prevention, and direct researchers for discovering new areas of potential drug discovery.

Etiology of infection

Influenza infection

The transmission of influenza viruses takes place through contact and airborne transmission (Figure 1). Virus spreading takes place in the air in the form of small droplets which remain inactive for a longer time and could infect the lower respiratory tract when inhaled. It has been found that human influenza viruses attack non-ciliated epithelial cells of the respiratory epithelium. They use sialic acid as their receptor and replicate within the infected cell nucleus by stealing the methylated cap of host messenger ribonucleic acid (mRNA). Influenza viruses' incubation period is about 1-2 days and during it, the virus infects, replicates, and spreads to infect other cells. Influenza virus strains responsible for pandemics, usually derived from the avian reservoir through an intermediate host like swine where they obtain lethal mutations.

COVID-19 infection

SARS-CoV-2 shares 88% of nucleotide sequences with two bat-derived coronaviruses as revealed in genomic analysis hence the name SARS-CoV-2. Presently, it appears that bats might host COVID-19 at first, but animal to the human transmission might have occurred when pangolin or other animals have been consumed by humans available at the seafood market of Huanan in China as the first case was reported in China (4).

Human to human transmission happens through breathing droplets, or when an infected person sneezes or coughs or comes in contact with an infected surface (Figure 2). SARS-CoV-2 can remain viable on surfaces for about four days. Persons who are hypertensive, diabetic, immunocompromised, and affected with cardiovascular disease are more susceptible to COVID-19 infection.

Pathophysiology

(A) Infection to the respiratory system

As both the influenza virus (Figure 1) and coronavirus (Figure 2) are respiratory viruses they primarily infect the respiratory system through the respiratory tract.

(i) Influenza infection

The primary infection site for the influenza virus is the respiratory tract to reach the alveoli where it infects respiratory epithelial cells. Influenza virus can get away from host immune responses due to its high variability of HA glycoprotein and disperse throughout the body due to its NA glycoprotein which can break down sialic acid moieties. Attachment of viral surface protein hemagglutinin to sialic acids presented on the glycans of respiratory epithelial cells is the first step of infection. Then virus enters the cell by endosomes, uncoating occurs, viral negative-sense RNA is imported into the nucleus where it translates into viral particles by producing mRNA and replicates to form a high amount of negative-sense RNAs. The virus non-structural protein 1 (NSP1) blocks the innate immune system to recognize viral RNA and prevents the production of interferon-1 (IFN1) by infected cells (5). When IFN response fails, cells may induce apoptosis or programmed cell death for virus-infected cells however the virus has mechanisms to prevent that too. Acute respiratory distress syndrome (ARDS) can be a result of influenza infection because when the virus infects alveolar epithelial cells, it results in alveolar epithelial injury and failure of gaseous exchange.

(ii) SARS-CoV-2 infection

When SARS-CoV-2 reaches the respiratory tract it binds with the angiotensin-converting enzyme 2 (ACE2) receptor with its spike protein on human respiratory epithelial cells (6). Then membrane fusion occurs, naked viral RNA is released into the cell where it codes for polyproteins and forms transcription and replication complexes with virus-induced double-membrane vesicles. These complexes translate to form viral particles and RNAs which are assembled and released into the extracellular matrix. The reason why the viral RNA is not recognized by the host immune system is because of the NSP1 which hinders the IFN-1 response and cytokines production by degrading the host mRNA thus putting an end to the host translational system.

(B) Cytokine storm associated with viral infection

(i) Influenza

The most accepted possible pathophysiology mechanism

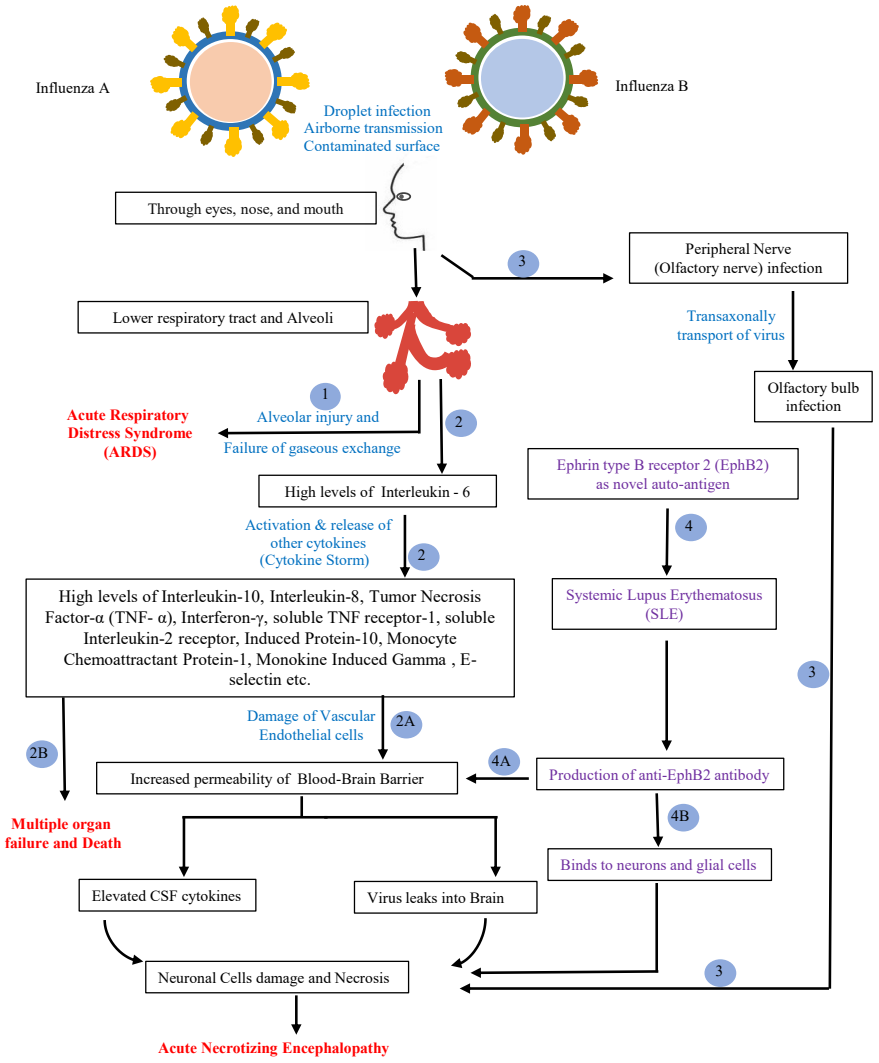

Figure 1 . Pathophysiology of influenza virus associated acute necrotizing encephalopathy.
Influenza A and influenza B viruses infect the respiratory tract through the nose, mouth and eyes. **(1)** Alveolar injury and failure of gaseous exchange lead to ARDS; **(2)** Virus can induce a cytokine storm by the IL-6 pathway that can either **(2A)** increase the permeability of BBB or **(2B)** multiple organ failure and death; **(3)** By transporting transaxonally virus can directly enter the nervous system and induce necrosis; **(4)** In Systemic Lupus Erythematosus caused by EphB2 antigen, the anti-EphB2 antibodies are produced which **(4A)** increase BBB permeability as well as **(4B)** cause neuronal cell damage. CSF cytokines levels are elevated and the virus can leak into the brain following the increased permeability of BBB resulting in neuronal necrosis ultimately leading to Acute necrotizing encephalopathy .

of ANE is virus-induced cytokine storm (Figure 1). Ichiyama et al studied 15 patients with influenza virus-associated encephalopathy and reported that patients who had a high interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and soluble TNF receptor 1 (sTNFR1) levels in cerebrospinal fluid (CSF) or serum displayed poor outcomes and four of these patients had neurologic sequelae. Upon post mortem examinations they found vascular damage with the leaking of plasma protein into the brain and spinal cord (7).

When serum cytokine concentrations of a boy diagnosed with influenza-associated ANE were compared with control samples of influenza-infected children without encephalopathy, very high levels of IL-6 and interleukin-10 (IL-10) were found along with slightly elevated levels of TNF-α, sTNFR1, IFN-γ, soluble interleukin-2 receptor (sIL2R), and E-selectin (8). These all results indicate neuronal cell damage, necrosis in neuronal cells, increase permeability of vascular EC, and damage in it.

(ii) COVID -19

After SARS-CoV-2 infection the cytokine release syndrome has been reported (Figure 2). The activation of monocytes, macrophages, and dendritic cells occurs when respiratory epithelial cells get infected by SARS-CoV-2. This results in the release of proinflammatory cytokines like IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) from Th1 cells, IL-6 and its soluble receptor stimulate other cell types like endothelial cells indirectly, directing a storm of cytokine production which is associated with ARDS (9). The inflammatory monocytes are activated by the GM-CSF to release a large

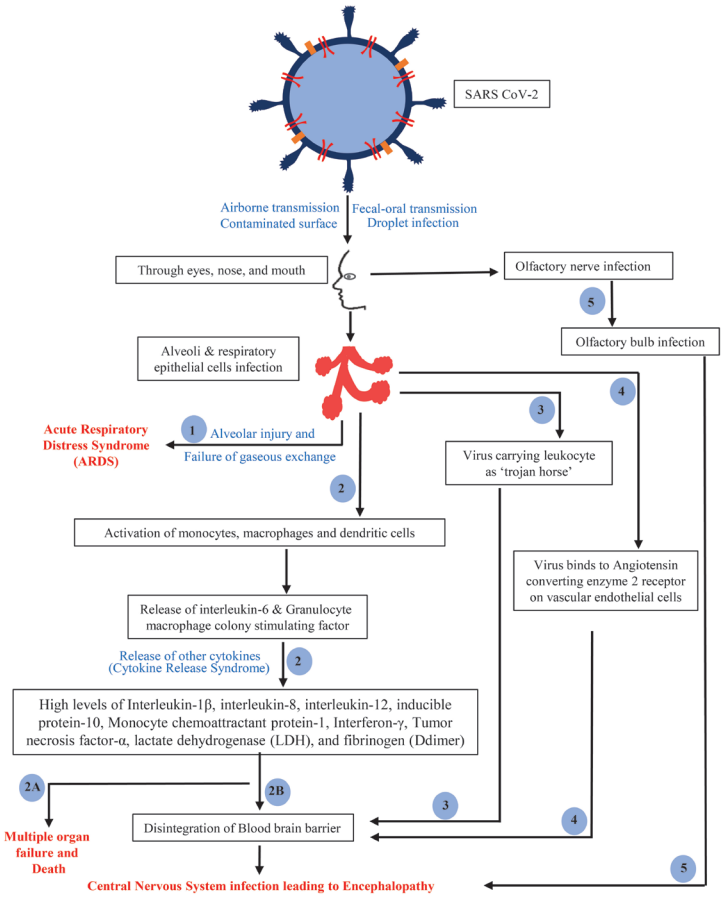

Figure 2. Pathophysiology of COVID-19 Encephalopathy.
SARS-CoV-2 primarily affects the respiratory system entering through the eyes, nose, and mouth. **(1)** Alveolar injury and failure of gaseous exchange due to viral infection lead to ARDS; **(2)** Due to viral infection activation of monocytes, macrophages and dendritic cells occur which initiate cytokine releasing cascade, called cytokine release syndrome; High levels of cytokines either result in **(2A)** multiple organ failure and death or **(2B)** disintegration of the BBB; **(3)** Virus carrying leukocyte could cross the BBB as a 'trojan horse' and induce brain damage; **(4)** Virus could bind to ACE 2 receptor on vascular endothelial cells that follow the disruption of BBB; **(5)** Virus could directly invade CNS through the olfactory nerve. All these conditions lead to neuronal infection and encephalopathy.

amount of IL-6, TNF-α, and other cytokines like IL-1β, IL-6, IL-8, IL-12, IP-10, MCP-1, and IFN-γ.

Microglial priming could be an associative factor responsible for cytokine storm. This is the condition when microglia multiplies, gets activated, and remains in priming condition. Priming microglia becomes more susceptible to an inflammatory stimulus like a bacterial or viral invasion. In severe COVID-19 patients, cytokine storm is thought to be the main reason for the progression of complications in multiple organs and death (10).

(C) Infection to the nervous system

(i) Influenza infection

The first neurological complications in association with influenza infection were reported in four pediatric patients during the 2009 pandemic. In the CSF of five out of seven patients with influenza-associated encephalopathy (IAE), influenza virus RNA was found (11) however, it is still debatable if the virus breaks through CNS. These observations implied that the virus can actively replicate in the neuronal cells. By infecting the nerve endings of olfactory receptor neurons in the nasal cavity the virus can transport transaxonally into the olfactory bulb of brain. There is a report that suggests, the H5N1 Avian influenza virus can induce encephalopathy and neurodegeneration by entering through peripheral nerves in animals (12).

Another possible pathophysiology was explained by Shirai et al in a 39 years old female diagnosed with ANE and neuropsychiatric systemic lupus erythematosus, an autoimmune disease. Ephrin type B receptor 2 (EphB2) was recognized as a novel autoantigen responsible for systemic lupus erythematosus by applying a serological identification system for autoantigens using a retroviral vector and flow cytometry technique (13). So, anti-EphB2 antibodies either may have damaged the vascular EC and disrupted the blood-brain barrier (BBB) or bound to neurons and glia, resulting in brain necrosis and neuronal dysfunction (13).

(ii) SARS-CoV-2 infection

In neuronal cells, the presence of the ACE2 receptor implies the possible infection of SARS- CoV-2. Either

through the cribriform plate, next to the olfactory bulb or by post systemic circulation, coronavirus may enter the CNS. As studied in a transgenic mouse model, the course of transmission of SARS-CoV-2 could have occurred through the olfactory bulb giving rise to CNS infection (14). Through the olfactory bulb, the virus can infect rhinencephalon and respiratory centers in the brainstem resulting in neurogenic respiratory failure. The endothelial cells of the blood capillaries express ACE2 receptor profusely in the brain as well, through which the virus gains access to dissolve the BBB and infects the brain (15). Additionally there is a report where the presence of SARS-CoV-2 has been confirmed in the CSF. According to a study in 2020, 36.4% of patients affected with COVID-19 showed neurologic complications and out of them, 14.8% showed impaired consciousness (16). During acute pulmonary infection due to COVID-19, hypoxia and toxemia condition can lead to systemic inflammatory response syndrome resulting in septic or toxic encephalopathy which may be the reason for impaired consciousness. Besides, ANE with hemorrhagic lesions in medial temporal lobes has been reported in a COVID-19 patient. Other encephalopathies associated with COVID-19 that have been described are hypoxic necrotizing leukoencephalopathy, posterior reversible leukoencephalopathy, diffuse leukoencephalopathy, and hypoxic-ischemic encephalopathy.

Diagnosis of influenza-associated ANE

(A) Clinical symptoms

Influenza symptoms are fever, headache, cough, myalgias, malaise, and chills that occur in the first two days of infection. Moreover, seasonal influenza can cause gastrointestinal complications in children. The identification of ANE is done by sudden onset of encephalopathy followed by quickly worsening neurological complications. ANE occurs mostly in children within the age of 6-18 months but is rarely seen in adults. The first symptoms appear as altered mental status within the first three days of influenza infection and after that rapidly worsening neural condition. Acute encephalopathy after a viral illness, worsening neurological damage, high CSF protein levels, absence of pleocytosis, neuroimaging results of bilateral symmetrical participation of the thalami, putamen, internal capsule, brainstem, cerebellum and periventricular white matter, high levels of serum transaminases with normal ammonia level and absence of other bacterial or viral infection are the diagnostic criteria proposed for ANE of childhood (17). An increase in serum aspartate aminotransferases, alanine aminotransferases, prothrombin levels has been found in a seven years old girl diagnosed with influenza-associated ANE and was reported to be the first case of brain death due to ANE in the United States (18). Raised intracranial pressure, herniation, and diabetes insipidus could happen further in influenza-associated ANE.

To confirm the presence of influenza infections different tests are performed in the laboratory like viral antigen test, positive viral culture, viral RNA reverse transcription polymerase chain reaction (RT-PCR), and hemagglutination inhibition test. Serological tests of herpes virus, parainfluenza, Mycoplasma, Varicella-zoster virus are also done to rule out other encephalopathies.

(B) Neuroimaging and electroencephalographic findings

Magnetic resonance imaging (MRI) and computed tomography (CT) neuroimaging are performed and electroencephalogram (EEG) has been done to confirm the encephalopathic condition. The CT of the brain of a female child with ANE showed thalamic swelling and hypodensity symmetrically. Her brain MRI showed hyperintensity and hemorrhage in thalami, Diffusion-Weighted imaging and apparent diffusion coefficient (ADC) showed symmetrical putamen hyperintensity, caudate restriction, symmetric restriction of hippocampi, amygdala, and pons. Fluid attenuated inversion recovery images showed hyperintensity of dorsal pons and vermis in her brain implying cytotoxic edema and vasogenic edema (19). In an infant diagnosed with influenza-associated ANE, EEG results appeared medium to high voltage delta activity superimposed with beta activity (20). Her CT scan indicates edema with lesions in the white matter of bilateral frontal lobes and deep right parietal lobe. Symmetrical high signal intensity lesions in the subcortical white matter of thalami and frontoparietal lobe bilaterally were observed in an MRI scan of a six years old boy diagnosed with ANE by novel influenza (H1N1) virus along with 2-4 Hz delta-theta wave slowing in electroencephalography. ANE with involvement of meninges and spinal cord have been reported in a two years old girl where background electric activity of medium-high voltage theta-delta waves was revealed in EEG.

Diagnosis of COVID-19 encephalopathy

(A) Clinical symptoms

After a COVID-19 infection, the incubation lasts for 5 days, and for 11.5 days symptoms occur. The most common symptoms are fever, tiredness, dry cough, and less common symptoms are sore throat, diarrhea, headache, conjunctivitis, body pain, loss of taste or smell, skin rashes, or discoloration of fingers/toes according to the WHO. Gastrointestinal complications like diarrhea, vomiting, and anorexia have been reported in 40% of affected individuals with COVID-19. In a severe progression of the disease elevated lactate dehydrogenase, aspartate and alanine aminotransferases, creatine kinase plus myoglobin, creatine phosphokinase, and D-dimer could be found. Agitation, delirium, hypogeusia/dysgeusia, hyposmia/anosmia, and seizures are the symptoms of SARS-CoV-2 invasion to the brain. Out of all the severe neurological complications due to COVID-19, seizures occupy the highest peak in most cases i.e. around 57%. Andriuta et

al reported two cases of COVID-19 encephalopathy in a previously normal female and a middle-aged male with a history of type 2 diabetes, hypertension, and dyslipidemia. Both have a positive test for viral nucleoproteins in the CSF, normal cytology, normal glucose, elevated CSF protein levels, and the presence of antibodies in CSF (21). The female patient showed motor impairment of lower limbs, hypo-pallesthesia of four limbs, bladder and bowel incontinence.

In France, four patients were diagnosed with COVID-19 related encephalopathy based on brain 2-deoxy-2-fluoro-D-glucose (FDG)-positron emission tomography (PET)/CT imaging and MRI. All of them had a confirmed RT-PCR positive of SARS CoV-2 infection and showed neurological symptoms of psychomotor agitation, psychomotor slowing, frontal lobe syndrome, cerebellar syndrome, anxiety and one of them had cerebellar ataxia too. In some cases of COVID-19 infection, isolated multiple cranial neuropathies which is a mild spectrum of Miller-Fischer syndrome have been reported. Neuropsychiatric symptoms like delirium, mild cognitive impairment, mood swings, insomnia, suicide, and psychosis have been reported in COVID-19 individuals. In addition, COVID-19 related hemorrhagic ANE has been reported in a 69-year-old female having aplastic anemia based on hemorrhagic lesions in the brainstem seen in CT and MRI results.

The presence of SARS-CoV-2 infection can be confirmed by RT-PCR test and CT scan of the chest with an efficiency of around 70% and 98% respectively. Immunological tests like immunofluorescence assay, direct fluorescence antibody test, microneutralization assay, and nucleocapsid protein detection assay could be done for a quick and profitable test.

(B) Neuroimaging and electroencephalographic findings

In 2020 two cases of COVID-19 have been reported in which one is a middle-aged female and another one is a middle-aged male. Chest CT of the female patient showed bilateral interstitial pneumonia of the thorax and MRI was normal for spinal cord while non-contrasted enhanced MRI of brain showed hyperintensity in the mesencephalon. The male patient showed diffused hyperintensities in white matter bilaterally with a normal ADC during MRI and intense hemorrhagic lesions in both pallidi during Gadolinium contrast-enhanced MRI (21). A 74-year-old male was diagnosed with COVID-19 infection with a prior history of embolic stroke and gradually it developed into encephalopathy. CT scan showed no abnormalities, and EEG showed sharp countered waves with a focal slowing in left temporal regions.

Treatment

(A) For influenza-associated ANE

Antiviral drugs, anti cytokines, and mild hypothermia therapy are possible treatments that can be used for ANE however, it is preferable to use antivirals in patients with neurological complications following influenza infection. Oseltamivir, zanamivir, peramivir are three antiviral drugs approved by Food and Drug Administration (FDA) that are recommended for influenza infection. The infusion of intravenous immunoglobulins (IVIg) at 400 mg/kg/d along with oseltamivir has been reported to be effective for a four and half years girl with ANE in lowering symmetrical lesions of the brain (19). The patient's temperature is lowered down to about 34°C for three days and gradually increased at a rate of 1°C per day for three days in mild hypothermia therapy. For suppressing cerebral edema and protecting the brain from brain injury, this therapy is quite efficacious (22). The successful treatment of influenza B-associated ANE has been reported in a middle-aged female patient by administrating methylprednisolone initially and oseltamivir, IVIg therapy, and levetiracetam in the later stage. ANE has a mortality rate of 30% and 10% affected get complete recovery. The recovered individuals in most cases showed acquired brain injury and become neurologically handicapped. Immunotherapy was found to be effective against ANE and monoclonal antibody therapy can be administered as a treatment. To prevent influenza infection currently, egg or cell-cultured inactivated subunit vaccines are used intramuscularly which is yearly being changed on the guidance of WHO.

(B) For COVID-19 Encephalopathy

As SARS-CoV-2 is known to attach with ACE2, losartan, an angiotensin receptor 1 blocker (ATR1) has been suggested for lowering the infection. IFN with ribavirin-like recombinant compounds has a restricted effect on COVID-19 infection. Presently treatment with remdesivir, a novel nucleotide analog prodrug that was earlier used for Ebola virus disease along with specific monoclonal antibodies is being used for coronavirus infection. Administration of pulse corticosteroids and intravenous polyvalent IVIg has shown a gradual improvement from neurological complications of COVID-19 encephalopathy in four patients and antidepressant or anti-epileptic drugs can be given based on the symptoms of patients. Recently hydroxychloroquine has shown antiviral activity by binding to sialic acids and reducing glycosylation of ACE2 receptor results in non-binding of spike protein to ACE2 receptor (23). For inhibiting cytokine storm tocilizumab is found to be effective in severe COVID-19 patients by blocking the IL-6 signal transduction pathway. Although it is still uncertain that the discharged patients can carry live SARS-CoV-2 virus, proper monitoring of the patient after discharge is recommended. If they carry the virus, then they could be a new source of infection. Since now, restricted movement of people, rapid testing after isolation, and profoundly operational health care services have controlled the spreading and mortality to some extent.

Familial or recurrent cases

(A) Recurrent influenza-associated ANE

Rare recurrent cases of ANE have been described, termed as acute necrotizing encephalopathy type 1 (ANE1) with mutations in RANBP2, a nuclear pore protein gene on chromosome 2q11-13. The protein coded by the RANBP2 gene has a vital role in neuronal cell's energy metabolism however it is still unclear how mutations in RANBP2 gene affect the patient. The formation of CNS lesions and spinal cord lesions are more distributed in familial cases of ANE. Singh et al in 2015 presented two cases of ANE1 in siblings, one aged two years seven months (case 1) and another one year four months (case 2). The 2-year child developed acute encephalopathy on the 5th day with a history of fever, dullness, and vomiting with a speculative viral infection while the younger one became encephalopathic after 1.5 years with clonic seizures. Both cases are initially diagnosed with ANE but later with ADEM and show elevated CSF protein levels in the second case, CT scan was normal in both, MRI showed T2 hyperintense signal in temporal and parietal lobes, cerebellar cortex, pons in both cases and middle cerebellar peduncle in the first case. Both children recovered with the administration of methylprednisolone and prednisolone and were confirmed for mutation in the RANBP2 gene (c.1880C>T: p.Thr585Met) (24).

Moreover, in the previous generation their father had the same mutation but showed no symptoms. According to a study, 89% of cases of ANE1 had c.1880C>T: p.Thr585Met mutation and 94% of cases had elevated CSF protein levels with no CSF pleocytosis (24). Testing of RANBP2 mutation should be done if any one of the following characters is present i.e., encephalopathy, recurring event in the victim, encephalopathy of previous generations, high CSF proteins with no pleocytosis, and neuroimaging findings of lesions in the brainstem, or changes in external capsule symmetrically/asymmetrically (24). Lately, familial ANE associated with RANBP2 mutation has been found to show an autosomal dominant inheritance with incomplete penetrance around 40% and can occur with rapid progression in children following viral infection.

Neilson et al studied thirty-five unrelated patients/families with ANE out of which sixteen had a missense heterozygous mutation at the 1880 position of complementary deoxyribonucleic acid (cDNA) derived from lymphoblast mRNA. Two families were reported where other than c.1880C→T missense mutations were found like c.2085C→T; p.Thr653Ile and c.2094A→G; Ile656Val (2). It is still unclear that if the virus is the causative agent for RANBP2 mutation in recurrent ANE, but the mutation can arise de novo as in the case of a Caucasian female along with her mother.

(B) Recurrent COVID-19 related neurologic complications

The familial occurrence of COVID-19 encephalopathy has not been reported yet however, the recurrence of SARS-CoV-2 infection has been reported by various researchers. The first case is reported in February 2020 where four Chinese patients tested re-positive in the course of their recovery. False RT-PCR results, intermittent virus shedding, viral reinfection/reactivation, or exposure to an infected environment are the possible causes for recurrent SARS-CoV-2 infection (25). According to International League Against Epilepsy (ILAE), there is an increased risk of frequency of seizures in COVID-19 patients with epilepsy. Although seizures can be taken as an initial symptom for COVID-19, there are no confirmed clinical cases where the SARS-CoV-2 is responsible for the severity of seizures. The reinfection or reactivation can cause hypoxic encephalopathy, cytokine storm, or cerebrovascular complications. It has been reported that reinfection of SARS-CoV-2 could trigger a rise in IL-6 level which in turn is associated with lowering of thresholds for seizures.

A comparative account of infection, pathophysiology and treatment of Influenza virus and Coronavirus-19 is given below in the Table 1.

Discussion

ANE and COVID-19 encephalopathy both are neurologic complications of respiratory virus infections, Influenza and SARS-CoV-2 respectively. Primarily, children (6-18 months group) are affected with ANE with a few adult cases reported in western countries, while COVID-19 encephalopathy predominantly occurs in adults. Both the viruses spreading through droplet infection first infect the respiratory system. A brief comparison between Influenza associated ANE and COVID -19 encephalopathy has been shown in Table 1.

The accurate pathophysiology of ANE is still unclear, but the cytokine storm hypothesis is most accepted (Figures 1 and 2). There is no concrete evidence that the influenza virus could directly invade the nervous system; however, virus invasion to brain tissue has been reported in hardly one or two cases and evidence of viral RNA presence in CSF of patients has been seen in very few cases. Pathophysiology of COVID-19 encephalopathy remains uncertain as well but CSF and cerebellar presence of viral nucleoprotein has been reported in a few patients. As both the viruses affect the nasal passage there are two possible pathways to enter the nervous system, one is through the peripheral nerve endings to olfactory bulb transaxonally and another is direct, by increasing the permeability of BBB. High levels of serum and/or CSF proinflammatory cytokines IL-6, IL-8, IL-10, IP-10, TNF-α, IFN-γ sIL2R, IL-12 occur in both encephalopathy (cytokine release syndrome) however elevated levels of D-dimer and lactate dehydrogenase levels are seen in COVID-19 encephalopathy. These cytokines increase the permeability of vascular EC thus providing a pathological route to cross BBB by the virus. SARS-CoV-2 normally binds to ACE2 receptor, expressing of ACE2 receptor on the surface

Table 1. Brief comparison between influenza-associated acute necrotizing encephalopathy and COVID-19 encephalopathy

Parameters	Influenza-associated ANE	COVID-19 Encephalopathy
Causative agent	Influenza viruses – Influenza A and B	COVID-19 or SARS-CoV - 2
Susceptible hosts	Children, immunocompetent adults and older age groups	All age groups, preferably hypertensive, diabetic and immunocompromised adults
Pathophysiology	First infection to the respiratory system, direct invasion of the neural system, cytokine storm, disruption of BBB	First infection to the respiratory system, direct invasion of the neural system, cytokine releasing syndrome, microglial priming, disruption of BBB
Cytokine markers	TNF-α, sTNFR-1, IL-6, IL-10 in serum and CSF	C-reactive protein, D-dimer, lactate dehydrogenase, IL-6 in serum
CSF nature	High protein levels, no pleocytosis	High protein levels, presence of antibodies
Neurological symptoms	Altered mental status, altered sensorium, progressive coma, seizures	Agitation, delirium, hypogeusia/dysgeusia, hyposmia/anosmia, and seizures
Neuroimaging	Thalamic swelling, symmetrical hypodensity, hyperdensity and hemorrhage in thalami, the white matter of pons, hyperintensity in thalami, pons, putamen	Diffused hyperintensities in the white matter of both pallidi, mesencephalon, and hemorrhagic lesions
EEG	Medium to high voltage theta - delta activity superimposed with beta activity	Sharp countered waves with a focal slowing in the left temporal region
Treatments	Antiviral drugs, anti-cytokines, mild hypothermia therapy, IVIg, methylprednisolone like steroids	Losartan, remdesivir, pulse corticosteroids, intravenous polyvalent IVIg, hydroxychloroquine, tocilizumab
Reoccurrence	Mutations in RANBP2 nuclear pore gene, autosomal dominant with incomplete penetrance (40%)	Reinfection and reactivation of SARS-CoV- 2
Complications of reoccurrence	Necrotic lesions in the thalamus symmetrically, insular cortex, internal capsule, temporal – medial lobes, pons, midbrain, and brainstem	Hypoxic encephalopathy, cytokine storm, cerebrovascular complications, increased seizures

ANE, acute necrotizing encephalopathy; COVID–19, coronavirus disease 19; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; BBB, blood-brain barrier; TNF-α, Tumour necrosis factor α; sTNFR1, soluble tumour necrosis factor receptor 1; IL-6, interleukin-6; IL-10; Interleukin-10; CSF, cerebrospinal fluid; EEG; electroencephalogram; RANBP2, Ran binding protein 2; IVIg, intravenous immunoglobulins.

of vascular EC supports the possible pathophysiology of COVID-19. Another possible pathophysiological mechanism of SARS-CoV-2 includes microglial priming and virus-carrying leukocytes crossing BBB and influenza virus include anti EphB2 antibody damaging vascular EC (13,15). The pathophysiology of both encephalopathies could have been better explained if CSF study of patients and brain autopsy study of dead individuals had been done. Characteristic features of ANE include CSF elevated protein levels, no pleocytosis, symmetrical lesions in both thalami, the white matter of putamen, dorsal pons, and vermis which can be confirmed by CT and MRI scan while in COVID-19 encephalopathy elevated CSF protein levels, lesions in both pallidi and MRI results of hyperintensity of mesencephalon are seen. The neurological symptoms of ANE mostly include altered mental status and COVID-19 encephalopathy includes seizures. Recurrent ANE could arise in some individuals with a missense mutation in the RANBP2 gene however, it is not clear that if the virus is responsible for the mutation. Recurrent SARS-CoV-2 infection could cause hypoxic encephalopathy.

Despite there being no accurate treatment options available for these diseases, different antiviral drugs in combination with other therapies (like anti-cytokines) occur to be fruitful in some patients. Oseltamivir, methylprednisolone, hypothermia therapy, and IVIg administration in ANE patients showed improved results. Losartan, remdesivir, hydroxychloroquine, tocilizumab, corticosteroids, and IVIg therapy along with monoclonal antibodies administration proved to be effective against COVID-19 encephalopathy.

Conclusion

ANE and COVID-19 encephalopathy should be categorized under severe neurologic disease, as due to poor prognosis, late diagnosis, and insufficient treatments these could be fatal and life-threatening. A proper study of brain, spinal cord, and CSF is required to understand the pathophysiology of these encephalopathies. Pathophysiology-directed drugs like a drug to regulate BBB permeability and to increase the immune response potential in nasal mucosa to contain the virus within the respiratory tract mucosa should be researched. Hypothermia therapy should be applied in COVID-19 encephalopathic patients as it is known to lower the inflammatory cytokine levels and is also quite effective in ANE. A way to the development and application of monoclonal antibodies against ANE should be explored because it responds to IVIg therapy and the use of monoclonal antibodies is proved to be effective in COVID-19 encephalopathic patients.

These single-stranded RNA viruses responsible for these neurologic conditions are capable of mutation at a higher rate and give rise to new variants that can cause pandemics like the '2009 influenza' and '2020 coronavirus'. Therefore it is recommended to have effective vaccination strategies

which can give rise to long-lived antibodies in the body to counteract viral infection. Presently mesenchymal stem cell therapy with pathogen-specific programming is being applied to minimize respiratory virus infection. Good ventilation, proper disinfection of hospital wards, toilet sanitation, hand hygiene, use of masks, and regulation of isolation wards must be done to avoid rapid viral spreading in aerosols and cover the virus outbreak.

Authors' contribution

Conceptualization: SS.
Methodology: BKD and SS.
Validation: All authors.
Formal analysis; SS and BKD.
Investigation: BKD and SS.
Resources: All authors.
Data curation: All authors.
Writing—original draft preparation: BKD.
Writing—review and editing: SS and BKD.
Visualization: BKD, SS and NM.
Supervision: SS.
Project administration: SS.
Funding acquisition: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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