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REVIEW ARTICLE

# SARS-CoV-2 Encephalitis *versus* Influenza Encephalitis: More Similarities than Differences

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**Abstract:** ***Background*:** From time to time, physicians face challenging diagnostic and therapeutic issues concerning the acute management of children with viral encephalitis.

***Objectives*:** The aim of this article is to provide an updated narrative review on the similarities and differences between SARS-CoV-2 and influenza encephalitis.

***Methods*:** A PubMed search was performed with the function "Clinical Queries" using the key terms "SARS-CoV-2" OR "Influenza" AND "Encephalitis". The search strategy included meta-analyses, clinical trials, randomized controlled trials, reviews and observational studies. The search was restricted to the English literature and pediatric population. This article compares similarities and contrasts between SARS-CoV-2 and influenza-associated encephalitis.

***Results*:** Encephalitis is an uncommon manifestation of both influenza and SARS-CoV-2. Both viruses are associated with fever and respiratory symptoms. However, SARS-CoV-2 patients may only have mild symptoms or be asymptomatic as silent carriers, rendering the disease spread difficult to control. Influenza patients usually have more severe symptomatology and are often bed bound for several days limiting its spread. Influenza is associated with seasonal and annual outbreaks, whereas SARS-CoV-2 has become endemic. Complications of encephalitis are rare in both viral infections but, when present, may carry serious morbidity and mortality. Many long-term sequelae of COVID-19 infections (long COVID-19) have been described but not with influenza infections. Mortality associated with encephalitis appears higher with influenza than with SARS-CoV-2. Prophylaxis by immunization is available for both influenza and SARS-CoV-2. Specific efficacious antivirals are also available with oseltamivir for influenza and nirmatrelvir/ritonavir for SARS-CoV-2. Steroids are indicated with more severe SARS-CoV-2 but their role is not distinct in influenza disease.

***Conclusion*:** Encephalitis is a rare complication of influenza and SARS-CoV-2 infections. Both carry significant morbidity and mortality. Efficacious vaccines for prophylaxis and antivirals for treatment are available for both viruses.

**Keywords:** Encephalitis, SARS-CoV-2, COVID-19, influenza, mortality, immunizations, long COVID syndrome, oseltamivir, nirmatrelvir/ritonavir.

## 1. INTRODUCTION

From time to time, physicians face challenging diagnostic and therapeutic issues concerning the acute management of children presenting with symptoms of encephalitis. Entering the fourth winter of the COVID-19 pandemic, we have encountered several cases of SARS-CoV-2 and influenza encephalitis [1-3]. The SARS-CoV-2 and influenza viruses may even co-infect, especially in winter months, causing a more severe clinical picture [4]. We performed a review of the literature on SARS-CoV-2 and influenza encephalitis. A PubMed search was performed with the function "Clinical Queries" using the key terms "SARS-CoV-2" OR "Influenza" AND "Encephalitis". The search strategy included meta-analyses, clinical trials, randomized controlled trials, reviews and observational studies, and was restricted to the English literature and children. The search

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**Table 1. SARS-CoV-2 *versus* influenza encephalitis syndromes.**

| - | SARS-CoV-2 | Influenza A |
|---|---|---|
| **Symptomatology** | ➢ Develops over hours to days and manifests as personality, behavioural, conscious or cognitive changes [51].<br>➢ Fever, headaches [15].<br>➢ Altered mental status and seizures also occur in patients with COVID-19 encephalitis. | ➢ Fever, headache.<br>➢ Seizures and altered consciousness [55].<br>➢ Acute non-inflammatory encephalopathy presenting with seizures and coma may occur [17, 62].<br>➢ Specific acute encephalopathy syndromes: acute necrotizing encephalopathy, mild encephalopathy with reversible splenial lesion, acute encephalopathy with biphasic seizures and late diffusion restriction, and hemiconvulsion-hemiplegia syndrome [16]. |
| **Prevalence** | ➢ Encephalitis occurs in approximately 0.003% of pediatric COVID-19 cases in one report [2].<br>➢ 0.2% in a systematic review and meta-analysis [1].<br>➢ Encephalitis occurs more frequently in patients with severe COVID-19 [5].<br>➢ Encephalitis in 7% hospitalised patients with COVID-19 in Wuhan, China, and 69% of patients in intensive care with COVID-19 in France [12]. | ➢ Encephalitis in 1.4% hospitalized patients with influenza [16].<br>➢ The mean annual incidence was 2.8 per 100,0000 among Australian children aged ≤14 years [16].<br>➢ Peak incidence was between 6 and 18 months of age [62]. |
| **Transmission** | ➢ Person-to-person, zoonosis [63-65] | ➢ Person-to-person, zoonosis [63-65] |
| **Diagnostic tests** | ➢ Diagnostic criteria for COVID-19-related encephalitis were not well established [41].<br>➢ Possible encephalitis can be suspected in patients with SARS-CoV-2 detected in respiratory or other non-CNS samples, with no other cause found to explain the CNS affection [12].<br>➢ CSF can be normal or may reveal elevated protein and pleocytosis [13].<br>➢ SARS-COV2 could be isolated in only a few cases [15, 41].<br>➢ Magnetic resonance imaging abnormalities were found in 92.0% with an intracranial vessel gadolinium enhancement in 85% of patients, while an increased CSF/serum quotient of albumin suggestive of disruption of the blood-brain barrier was reported in 86% [15].<br>➢ EEG with nonspecific changes and near-physiological patterns [13]. | ➢ Culture, antigen test, PCR of respiratory secretions [45].<br>➢ Cranial MRI in 3 cases displayed multifocal lesions in the thalami, brainstem and cerebellar hemisphere. MRI demonstrated reversible splenial lesion in the corpus callusumin. EEG tracings were characterized by diffuse slow wave activity in 4 cases, and status epilepticus in 1 case [55].<br>➢ Neuroimaging shows cerebral oedema in most cases, but around 10-20% will show features of ANE or acute necrotising encephalopathy [17]. |
| **Treatment** | ➢ COVID-19-related encephalitis responsive to high-dose glucocorticoids [5, 50, 51].<br>➢ IV methylprednisolone 500mg iv for 3 days with good effects in an adult [5].<br>➢ Antivirals: Early use of nirmatrelvir/ritonavir in mild cases. Remdesivir in severe cases. | ➢ Mannitol can be given, an external ventricular drain can be placed, and a posterior fossa craniectomy can be performed in case of high intracranial pressure [10].<br>➢ Empirical early use of oral oseltamivir (Tamiflu) [11].<br>➢ Intravenous immunoglobulin and/or methylprednisolone for severe cases [3, 55]. |
| **Prognosis** | ➢ Very low mortality rate, the estimated mortality rate was 0.0002% without encephalitis.<br>➢ The average mortality rate of encephalitis in COVID-19 patients was 13.4% in one study [1].<br>➢ Possible high mortality, but no exact epidemiology has been citedfor COVID-19 encephalitis [2, 12, 13, 66].<br>➢ Approximately 51% of children survived without detectable neurologic sequelae.<br>➢ Life-thretenting presentations are rare but can include severe encephalopahty, stroke, acute fulmiant cerebral edema [67]. | ➢ Significant neurologic morbidity occurred in 54% of an Australian study [16]<br>➢ 20-30% fatality [2, 17]<br>➢ Persisting neuro disability in around one-third of survivors is associated with cerebral atrophy [17] |

was restricted to the English literature and patients ≤ 18 years of age to familiarize physicians with the management of children with SARS-CoV-2 and influenza encephalitis in the upcoming winter and beyond (Table **1**).

## 2. PATHOGENESIS

SARS-CoV-2 and influenza viruses first invade the human body and replicate outside the CNS (central nervous system). Encephalitis refers to inflammation involving the

brain parenchyma with resultant neurologic dysfunction, whereas encephalopathy refers to the disruption of brain function in the absence of an inflammation of the brain parenchyma. The two viruses are usually not found in the cerebrospinal fluid (CSF) of patients inferring that this is a parainfectious process. Upon infection, SARS-CoV-2 and influenza viruses could disseminate to the brain *via* the circulatory system. The causative virus as well as the host's inflammatory response, disrupts neural cell function, causing cerebral edema and bleeding. Extensive white blood cells and microglia in the CNS are commonly present in patients with encephalitis. Significant necrosis of nerve cells may be seen. In the two encephalitis syndromes (ES) caused by SARS-CoV-2 and influenza viruses, the CNS may be severely affected in a minority of cases [5]. Encephalitis due to COVID-19 may be caused by the proinflammatory cytokine storm or rarely direct viral invasion in the CNS; a similar cytokine release state is seen in influenza infections, causing cytokine storms in our bodies [5, 6].

## 3. CLINICAL FEATURES

Symptoms of encephalitis usually occur abruptly and include fever, altered mental status, headache, decreased level of consciousness, unusual behavior, hallucinations, confusion, personality change, sensitivity to light, nausea, vomiting, and, in severe cases, paralysis, seizures and coma [7, 8]. In an infant, a tense or bulging fontanelle indicates increased intracranial pressure [9, 10]. Severe symptoms more commonly occur among infants and the elderly. The clinical features of encephalitis caused by SARS-CoV-2 and influenza are similar. A meticulous history and a comprehensive physical examination are essential to guide the management of children with encephalitis [11].

The incidence of COVID-19 encephalitis varies depending on the season of the study [12-15]. Encephalitis occurs more frequently in patients with severe COVID-19 [5]. Encephalitis occurs in approximately 0.003% of pediatric COVID-19 cases [2]. Encephalitis was reported in 7% of hospitalised patients with COVID-19 in Wuhan, China, in early 2020, and 69% of patients in intensive care units with COVID-19 in France [12]. The local Hong Kong data suggest that the incidence of encephalitis associated with SARS-CoV-2 is low in children, but the mortality may be significant [2]. In Hong Kong, the incidence of encephalitis as a complication of COVID-19 in the general population was 0.2% (95% confidence interval [CI] = 0.056-0.44%). The average mortality rate of encephalitis in COVID-19 patients was 13% (95% CI = 3.8%-26%) [1].

There has been no direct comparison with influenza encephalitis but a low incidence of encephalitis and significant mortality is also observed. Death or significant neurologic sequelae occurred in 54% of patients reported by an Australian study [16]. Fatality occurs in approximately 20-30% of patients with influenza encephalitis [2, 17]. Persisting neuro disability is reported in around one-third of survivors with influenza encephalitis, associated with cerebral atrophy [17]. One study reports no difference in hospitalization rates, admission rates to intensive care unit and rates of mechanical ventilator use between patients with COVID-19 and influenza [18]. The incubation period for COVID-19 depends on the variants. The most recent Omicron variants have shorter incubation periods. In a 2022 systematic review and meta-analysis of 142 studies with 812 patients, the pooled incubation period of COVID-19 was 6.57 days (95% confidence, 6.26 to 6.88). The mean incubation period of COVID-19 caused by the Alpha variant, Beta variant, Delta variant, and Omicron variant was 5 days, 4.5 days, 4.4 days, and 3.4 days respectively [19]. A person typically develops symptoms about 5 days after an infectious exposure to SARS-CoV-2 (except for the Omicron variant). On the other hand, the incubation period of influenza is typically between 1 and 4 days.

An individual is contagious for about a full day before symptoms appear for both COVID-19 and influenza. The infectivity period tends to be longer with SARS-CoV-2 than with influenza [20]. Older children and adults with influenza appear to be most contagious during the first three to four days but may remain contagious for approximately seven days of their illness. Patients infected with SARS-CoV-2 remain infectious for ten days after symptoms first appear. The virus is detectable for much longer in some patients; however, transmission in these cases is questionable.

The clinical features of SARS-CoV-2 and influenza are similar and include fever, sore throat, coryza, chills, cough, fatigue, headache, and occasionally diarrhea and vomiting [21-25]. Infection with SARS-CoV-2 is unique in that some infected individuals with COVID-19 develop the symptoms of anosmia and/or hypogeusia. Children with COVID-19 are at unique risk for the multisystem inflammatory syndrome in children (MIS-C), especially those with immunodeficiency or asthma [23, 26-31]. More pediatric patients with SARS-CoV-2 than those with influenza develop MIS-C in the US [32, 33]. Interestingly, MIS-C is less often diagnosed among Asian children [27, 34]. Asymptomatic infection is more common in children with SARS-CoV-2 (especially with the Omicron variant) than in children with influenza. Children are less likely to be hospitalized than adults with COVID-19 and more likely to have mild or asymptomatic symptoms [23, 25, 28, 35-37]. Mortality rates of children infected with COVID-19 are low [38]. Mitigation efforts for the influenza pandemic or epidemics are not as extensive as those for the SARS-CoV-2. Children with influenza generally do not need to be strictly isolated.

The so-called “long COVID” syndrome describes many conditions in patients recovered from COVID-19 infection. However, many of these symptoms are vague and could also occur in patients with other severe respiratory tract infections [3]. The lack of pre-morbid information in most patients also makes “long COVID” difficult to define and delineate. More research is required to delineate better these symptoms in COVID-19 patients, especially those with encephalitis. In contrast, long-term sequelae of influenza “long influenza” have not been described.

## 4. INVESTIGATIONS

CSF for microbiologic investigations, protein and glucose, measurement of opening and closing pressures, and

radiologic imaging are important but should not defer resuscitation and prompt antiviral administration [11, 39, 40]. In most cases, the viral diagnosis is readily made in respiratory secretions by rapid antigen testing and polymerase chain reaction (PCR) [4]. A lumbar puncture before imaging studies might be contraindicated in the presence of a suspected increase in intracranial pressure, focal neurologic signs and seizures. An elevated protein level of ≥2.4 g/L in the CSF and high serum levels of aminotransferase are characteristic of acute necrotizing encephalopathy (ANE). Computed tomography (CT) of the brain reveals bilateral hypodensities of the cerebellum and thalamus, with diffuse edema and brainstem compression and a triventricular hydrocephalus. Cerebral abnormalities can be detected by magnetic resonance imaging (MRI) in a significant number of patients with encephalitis. In one study of patients with SAR-CoV-2 encephalitis managed at the Geneva University Hospitals, MRI abnormalities of the brain were found in 92% of patients [15]. Gadolinium enhancement of intracranial vessels was observed in 85% of patients. An increased CSF to serum quotient of albumin that is suggestive of disruption of the blood-brain barrier was reported in 85.7% of patients [15]. The above tests can be used to diagnose encephalitis but cannot differentiate SARS-CoV-2 encephalitis from influenza A encephalitis.

The brain histology of deceased patients with viral encephalitis shows dead neurons with nuclear dissolution and hypereosinophilia; and perivascular inflammatory cells, such as microglia, macrophages, and lymphocytes. Virions within neurons may be seen under electron microscopy [7]. Fatal cases of acute fulminant cerebral edema where the CSF were negative for SAR-CoV-2 have been reported, suggesting a para-infectious process is involved. SAR-CoV-2 has also been isolated from the CSF in approximately 6% of cases. Therefore, direct invasion of the brain parenchyma is also responsible in a small number of cases.

## 5. DIFFERENTIAL DIAGNOSES AND DIAGNOSIS

Differential diagnoses of these two viral encephalitis include autoimmune or paraneoplastic diseases such as anti-NMDA receptor encephalitis, cerebral abscess, tuberculosis, drug-induced delirium, drugs or toxins exposure, neurosyphilis, cerebral vascular disease, metabolic disease, and encephalitis from bacterial, fungal, protozoal, or parasitic worm infection [5-7] In children, the clinical features of viral encephalitis, acute disseminated encephalomyelitis (ADEM), as well as immune-mediated encephalitis, are similar [7]. As such, other diagnostic investigations and methodologies are needed to differentiate viral encephalitis from immune-mediated inflammatory CNS diseases.

The diagnosis of COVID-19 and influenza infection is often based on the constellation of clinical features of the respective infection, epidemiologic data and specific viral testing. COVID-19 encephalitis and influenza encephalitis should be suspected in patients with features of encephalitis and detection of SARS-CoV-2 or influenza virus, respectively, in the CSF, respirator or other non-CNS samples [12, 41, 42]. CSF examination can be normal or reveal elevated protein level, normal glucose level and /or pleocytosis [13] SARS-CoV-2 RNA could be detected only in a minority of cases. In one study of 304 patients with COVID-19 encephalitis whose CSF was tested for SARS-CoV-2 with PCR, only 17 (6%) patients were tested positive [43] Likewise, the chances of isolating influenza in CSF are low. Electroencephalogram (EEG) often shows nonspecific changes [13]. Etiologic diagnosis of encephalitis caused by SARS-CoV-2 and influenza can be based on the detection of the respective virus with rapid antigen testing or PCR of the CSF or respiratory secretion [44, 45].

## 6. MANAGEMENT

Treatment of encephalitis caused by SARS-CoV-2 or influenza is primarily supportive and supplemented with antiviral therapy. Individuals with encephalitis often require intensive care for frequent neurological examinations (including the use of the Glasgow Coma Scale score to quantify the level of consciousness), respiratory support, correction of fluid and electrolyte disturbance, renal and hepatic dysfunction, autonomic dysregulation, seizures, and non-compulsive status epilepticus [7].

Specifically, COVID-19 and Influenza can be treated with specific antivirals in the early stage of the illness. Early oral administration of oseltamivir (Tamiflu), a neuraminidase inhibitor, is recommended in treating more severe influenza disease, including encephalitis [46-48]. In December 2021, emergency use of oral nirmatrelvir/ritonavir for the treatment of COVID-19 was granted in the United States; Canada, the European Union and the United Kingdom followed suit with full authorization soon after. One study showed that oral nirmatrelvir/ritonavir reduced death and the risk of hospitalization by 88% [49]. Viral resistance rarely occurs. Studies have shown that COVID-19-related encephalitis is responsive to high-dose glucocorticoid steroids [5, 50, 51]. Some practical points are provided by the American College of Physicians, primarily for outpatient treatment of adults with COVID-19 [52]. Nirmatrelvir-molnupiravir ormolnupiravir should be considered to treat patients with mild-to-moderate SARS-CoV-2 in the outpatient setting who are within five to seven days of the onset of symptoms and at high risk for progression to severe disease. Remdesivir should be considered to treat patients with confirmed mild-to-moderate SARS-CoV-2 in hospital settings who are within 7 days of the onset of symptoms and at high risk for progressing to severe disease.

Elevated intracranial pressure might be relieved with the use of steroids, mannitol or hypertonic saline, but there is limited data on the efficacy of these treatments for viral encephalitis. Seizures can be treated with phenytoin or valproic acid. Status epilepticus may require treatment with benzodiazepines. Seizures and status epilepticus can be treated by appropriate selection of antiepileptic medications tailored to the clinical situation, patient characteristics and comorbidities. Short-term use of antipsychotic medications may be needed if behavioral alterations are present. Given

the possibility of complications that may develop from any viral encephalitis, a multidisciplinary team consisting of physicians, rehabilitation specialists, and speech therapists are important for the management of these patients [7]. The use of high-dose glucocorticosteroids in influenza-related encephalitis remains controversial. Empirical steroid usage has been reported with inconsistent results [3, 53-56].

The virus activates an immune-mediated reaction that causes encephalitis in a significant portion of those patients for which immunomodulatory treatment could provide benefits [6-9].

## 7. PROGNOSIS

If treated, individuals with COVID-19 encephalitis and influenza encephalitis often recover without long-term sequelae. In one study of 99 children with encephalitis at a mean follow-up of 35.6 months, only 51% of children survived without detectable neurologic sequelae. Some individuals may have developmental delay, difficulty concentrating, learning problems, behavior problems, speech disorders, memory loss, visual deficit, or motor deficit following encephalitis. Rarely individuals remain in a vegetative state that may become persistent or permanent. The most common long-term complication of viral encephalitis is seizures that may occur in ten to twenty percent of patients over several decades. Seizures resulting from viral encephalitis are generally resistant to medical therapy [7, 57-61].

## CONCLUSION

In summary, encephalitis is a rare and severe complication of SARS-CoV-2 and influenza infections that are associated with significant morbidities and mortalities, and both share a very similar presentation. Diagnosis of the viral etiology is readily made with PCR testing of respiratory specimens, as the yield of isolating SARS-CoV-2 or influenza in the CSF is low. Specific antivirals are available for both the treatment of COVID-19 and influenza infection and should be administered promptly for suspected encephalitis. Steroids might be useful for the management of more severe infections. Prophylaxis for these severe complications with vaccines for SARS-CoV-2 and influenza is readily available for children and should be advocated by healthcare professionals to increase the vaccination update rate. Encephalitis caused by both viruses may be associated with severe sequelae and mortality.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| ADEM | = | Acute Disseminated Encephalomyelitis |
| CNS | = | Central Nervous System |
| COVID-19 | = | Coronavirus Disease 2019 |
| CSF | = | Cerebrospinal Fluid |
| ES | = | Encephalitis Syndromes |
| LP | = | Lumbar Puncture |
| NMDA receptor | = | N-methyl-D-aspartate Receptor |
| SARS | = | Severe Acute Respiratory Syndrome |
| SARS-CoV-2 | = | Severe Acute Respiratory Syndrome-Coronavirus2 |

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

Professor Alexander K.C. Leung is a section editor of Current Pediatric Reviews.

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## REFERENCES

[1] Hon KL, Leung AKC, Leung KKY, Wong AHC. Impact of "long covid" on children: Global and Hong Kong perspectives. Curr Pediatr Rev 2022. http://dx.doi.org/10.2174/1573396319666221021154949 PMID: 36281870

[2] Hon KL, Tan YW, Leung KKY, *et al.* Pediatric COVID-19 acute encephalopathy and mortality. Curr Pediatr Rev 2022. http://dx.doi.org/10.2174/1573396318666220617161606 PMID: 35718976

[3] Hon KL. Successful treatment of influenza A encephalopathy. Hong Kong Med J 2020; 26(2): 154. http://dx.doi.org/10.12809/hkmj208417 PMID: 32300080

[4] Yilmaz H. Investigation of respiratory tract coinfections in Coronavirus disease 2019 infected and suspected cases. North Clin Istanb 2022; 9: 421-428. http://dx.doi.org/10.14744/nci.2022.82608

[5] Pizzato Tondo L, Beck Paglioli Neto E, Arpini S, Passos G, Becker J. Encephalopathy due to COVID-19 with great response to glucocorticoids. Cureus 2021; 13(9): e17845. http://dx.doi.org/10.7759/cureus.17845 PMID: 34660051

[6] Hon KL, Leung AKC, Leung WH, Leung KKY, Cheong KN, Lee PPW. Drugs for paediatric hyperinflammatory syndromes. Drugs Context 2022; 11: 1-11. http://dx.doi.org/10.7573/dic.2022-2-1 PMID: 35720057

[7] Costa BK, Sato DK. Viral encephalitis: a practical review on diagnostic approach and treatment. J Pediatr (Rio J) 2020; 96(Suppl 1)(Suppl. 1): 12-9. http://dx.doi.org/10.1016/j.jped.2019.07.006 PMID: 31513761

[8] Islam MA, Cavestro C, Alam SS, Kundu S, Kamal MA, Reza F. Encephalitis in patients with COVID-19: A systematic evidence-based analysis. Cells 2022; 11(16): 2575. http://dx.doi.org/10.3390/cells11162575 PMID: 36010650

[9] Lin MC, Chi H, Chiu NC, Huang FY, Ho CS. Factors for poor prognosis of neonatal bacterial meningitis in a medical center in Northern Taiwan. J Microbiol Immunol Infect 2012; 45(6): 442-7. http://dx.doi.org/10.1016/j.jmii.2011.12.034 PMID: 22571998

[10] Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. Clin Perinatol 2015; 42(1): 29-45, vii-viii. http://dx.doi.org/10.1016/j.clp.2014.10.004 PMID: 25677995

[11] Alamarat Z, Hasbun R. Management of acute bacterial meningitis in children. Infect Drug Resist 2020; 13: 4077-89. http://dx.doi.org/10.2147/IDR.S240162 PMID: 33204125

[12] Ellul MA, Benjamin L, Singh B, *et al.* Neurological associations of COVID-19. Lancet Neurol 2020; 19(9): 767-83. http://dx.doi.org/10.1016/S1474-4422(20)30221-0 PMID: 32622375

[13] Garg RK, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: A review. J Med Virol 2021; 93(1): 206-22. http://dx.doi.org/10.1002/jmv.26207 PMID: 32558956

[14] Liotta EM, Batra A, Clark JR, *et al.* Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 2020; 7(11): 2221-30. http://dx.doi.org/10.1002/acn3.51210 PMID: 33016619

[15] Uginet M, Breville G, Assal F, *et al.* COVID-19 encephalopathy: Clinical and neurobiological features. J Med Virol 2021; 93(7): 4374-81. http://dx.doi.org/10.1002/jmv.26973 PMID: 33782993

[16] Britton PN, Dale RC, Blyth CC, *et al.* Influenza-associated encephalitis/encephalopathy identified by the australian childhood encephalitis study 2013-2015. Pediatr Infect Dis J 2017; 36(11): 1021-6. http://dx.doi.org/10.1097/INF.0000000000001650 PMID: 28654561

[17] Surtees R, DeSousa C. Influenza virus associated encephalopathy. Arch Dis Child 2006; 91(6): 455-6. http://dx.doi.org/10.1136/adc.2005.092890 PMID: 16714714

[18] Song X, Delaney M, Shah RK, Campos JM, Wessel DL, DeBiasi RL. Comparison of clinical features of COVID-19 *vs.* seasonal influenza A and B in US children. JAMA Netw Open 2020; 3(9): e2020495. http://dx.doi.org/10.1001/jamanetworkopen.2020.20495 PMID: 32897374

[19] Wu Y, Kang L, Guo Z, Liu J, Liu M, Liang W. Incubation period of COVID-19 caused by unique SARS-CoV-2 strains. JAMA Netw Open 2022; 5(8): e2228008. http://dx.doi.org/10.1001/jamanetworkopen.2022.28008 PMID: 35994285

[20] Pormohammad A, Ghorbani S, Khatami A, *et al.* Comparison of influenza type A and B with COVID-19: A global systematic review and meta-analysis on clinical, laboratory and radiographic findings. Rev Med Virol 2021; 31(3): e2179. http://dx.doi.org/10.1002/rmv.2179 PMID: 33035373

[21] Hon KL, Leung KKY, Hui WF, Ng DKK. Applying lessons from influenza pandemics to the COVID-19 pandemic. Pediatr Pulmonol 2021; 56(9): 3071-4. http://dx.doi.org/10.1002/ppul.25571 PMID: 34288587

[22] Hon KL, Leung KKY. From influenza to COVID-19 vaccinations: Counselling anxious parents about deaths following influenza immunizations in Korea. Pediatr Pulmonol 2021; 56(6): 1779-81. http://dx.doi.org/10.1002/ppul.25260 PMID: 33765351

[23] Hoang A, Chorath K, Moreira A, *et al.* COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine 2020; 24: 100433. http://dx.doi.org/10.1016/j.eclinm.2020.100433 PMID: 32766542

[24] Jeng MJ. Coronavirus disease 2019 in children: Current status. J Chin Med Assoc 2020; 83(6): 527-33. http://dx.doi.org/10.1097/JCMA.0000000000000323 PMID: 32502117

[25] Choi SH, Kim HW, Kang JM, Kim DH, Cho EY. Epidemiology and clinical features of coronavirus disease 2019 in children. Clinical and Experimental Pediatrics 2020; 63(4): 125-32. http://dx.doi.org/10.3345/cep.2020.00535 PMID: 32252139

[26] Ahmed M, Advani S, Moreira A, *et al.* Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine 2020; 26: 100527. http://dx.doi.org/10.1016/j.eclinm.2020.100527 PMID: 32923992

[27] Leung KKY, Hon KL, Wang MHT, Ng DDKK, Ip P. Paediatric multisystem inflammatory syndrome and COVID-19: another novel syndrome? Hong Kong Med J 2021; 27(2): 161-2. http://dx.doi.org/10.12809/hkmj208681

[28] Rajapakse N, Dixit D. Human and novel coronavirus infections in children: a review. Paediatr Int Child Health 2021; 41(1): 36-55. http://dx.doi.org/10.1080/20469047.2020.1781356 PMID: 32584199

[29] Sharma C, Ganigara M, Galeotti C, *et al.* Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. Nat Rev Rheumatol 2021; 17(12): 731-48. http://dx.doi.org/10.1038/s41584-021-00709-9 PMID: 34716418

[30] COVID-19: The impact on pediatric emergency care. Pediatr Emerg Med Pract 2020; 17(Suppl 6-1): 1-27.

[31] Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol 2020; 20(8): 453-4. http://dx.doi.org/10.1038/s41577-020-0367-5 PMID: 32546853

[32] Similarities and differences between flu and COVID-19. Available from: https://www.cdc.gov/flu/symptoms/flu-vs-covid19.htm

[33] Duarte-Salles T, Vizcaya D, Pistillo A, Casajust P, Sena AG, Lai LYH. Baseline characteristics, management, and outcomes of 55,270 children and adolescents diagnosed with COVID-19 and 1,952,693 with influenza in France, Germany, Spain, South Korea and the United States: an international network cohort study. MedRxiv 2020. http://dx.doi.org/10.1101/2020.10.29.20222083

[34] Chua GT, Xiong X, Choi EH, *et al.* COVID-19 in children across three Asian cosmopolitan regions. Emerg Microbes Infect 2020; 9(1): 2588-96. http://dx.doi.org/10.1080/22221751.2020.1846462 PMID: 33138739

[35] Shen K, Yang Y, Wang T, *et al.* Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020; 16(3): 223-31. http://dx.doi.org/10.1007/s12519-020-00343-7 PMID: 32034659

[36] Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J. SARS-CoV-2 infection in children. N Engl J Med 2020; 382(17): 1663-5. http://dx.doi.org/10.1056/NEJMc2005073

[37] Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics 2020; 145(6): e20200702. http://dx.doi.org/10.1542/peds.2020-0702 PMID: 32179660

[38] Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19. Pediatr Infect Dis J 2020; 39(5): 355-68. http://dx.doi.org/10.1097/INF.0000000000002660 PMID: 32310621

[39] Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management. NICE. 2015: Feb.ISBN-13: 978-1-4731-3040-1. (https://www.ncbi.nlm.nih.gov/books/NBK555182/)

[40] Paul SP, Kini PK, Tibrewal SR, Heaton PA. NICE guideline review: fever in under 5s: assessment and initial management (NG143). Arch Dis Child Educ Pract Ed 2021; 107(3): edpract-2021-321718. http://dx.doi.org/10.1136/archdischild-2021-321718 PMID: 34244233

[41] Berlit P, Bösel J, Gahn G, *et al.* "Neurological manifestations of COVID-19" - guideline of the German society of neurology. Neurological Research and Practice 2020; 2(1): 51. http://dx.doi.org/10.1186/s42466-020-00097-7 PMID: 33283160

[42] Pilotto A, 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 2021; 223(1): 28-37. http://dx.doi.org/10.1093/infdis/jiaa609 PMID: 32986824

[43] Lewis A, Frontera J, Placantonakis DG, *et al.* Cerebrospinal fluid in COVID-19: A systematic review of the literature. J Neurol Sci 2021; 421: 117316. http://dx.doi.org/10.1016/j.jns.2021.117316 PMID: 33561753

[44] Mögling R, Fischer C, Stanoeva KR, *et al.* Sensitivity of detection and variant typing of SARS-CoV-2 in european laboratories. J Clin Microbiol 2022; 60(12): e01261-22. http://dx.doi.org/10.1128/jcm.01261-22 PMID: 36445090

[45] Sanders PJLT, van Waardenburg DA, Vermeulen RJ. Influenza A-associated acute necrotising encephalopathy in a 10-year-old child. BMJ Case Rep 2020; 13(8): e233541. http://dx.doi.org/10.1136/bcr-2019-233541 PMID: 32843445

[46] Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. Curr Opin Neurol 2010; 23(3): 305-11.
http://dx.doi.org/10.1097/WCO.0b013e328338f6c9
PMID: 20455276

[47] Yen J, Al Moamen A, Margolesky J. Influenza B-associated encephalitis with rapid improvement with oseltamivir. Neurol Sci 2021; 42(2): 745-7.
http://dx.doi.org/10.1007/s10072-020-04793-9 PMID: 33047196

[48] Choi GJ, Park JY, Choi JS, *et al.* Influenza-associated neurologic complications in hospitalized pediatric patients. Pediatr Infect Dis J 2021; 40(12): e466-71.
http://dx.doi.org/10.1097/INF.0000000000003332
PMID: 34609108

[49] Hammond J, Leister-Tebbe H, Gardner A, *et al.* Oral nirmatrelvir for high-risk, nonhospitalized adults with covid-19. N Engl J Med 2022; 386(15): 1397-408.
http://dx.doi.org/10.1056/NEJMoa2118542 PMID: 35172054

[50] Pugin D, Vargas MI, Thieffry C, *et al.* COVID-19-related encephalopathy responsive to high-dose glucocorticoids. Neurology 2020; 95(12): 543-6.
http://dx.doi.org/10.1212/WNL.0000000000010354
PMID: 32680950

[51] Pilotto A, Odolini S, Masciocchi S, *et al.* Steroid-responsive encephalitis in coronavirus disease 2019. Ann Neurol 2020; 88(2): 423-7.
http://dx.doi.org/10.1002/ana.25783 PMID: 32418288

[52] Qaseem A, Yost J, Miller MC, Andrews R, Jokela JA, Forciea MA. Outpatient treatment of confirmed COVID-19: Living, rapid practice points from the american college of physicians (version 1). Ann Intern Med 2023; 176: 115-124.
http://dx.doi.org/10.7326/M21-3272 PMID: 36442061

[53] Nakano A, Yamasaki R, Miyazaki S, Horiuchi N, Kunishige M, Mitsui T. Beneficial effect of steroid pulse therapy on acute viral encephalitis. Eur Neurol 2003; 50(4): 225-9.
http://dx.doi.org/10.1159/000073864 PMID: 14634267

[54] Howard A, Uyeki TM, Fergie J. Influenza-associated acute necrotizing encephalopathy in siblings. J Pediatric Infect Dis Soc 2018; 7(3): e172-7.
http://dx.doi.org/10.1093/jpids/piy033 PMID: 29741717

[55] Li XF, Ai B, Ye JW, *et al.* [Clinical analysis of seven cases of H1N1 influenza-associated encephalopathy in children]. Zhonghua Er Ke Za Zhi 2019; 57(7): 538-42.
http://dx.doi.org/10.3760/CMA.J.ISSN.0578-1310.2019.07.009
PMID: 31269554

[56] Takia L, Saini L, Keshavan S, *et al.* Neurological manifestations of influenza A (H1N1): Clinical features, intensive care needs, and outcome. Indian J Pediatr 2020; 87(10): 803-9.
http://dx.doi.org/10.1007/s12098-020-03297-w PMID: 32358785

[57] Kim MG, Stein AA, Overby P, *et al.* Fatal cerebral edema in a child with COVID-19. Pediatr Neurol 2021; 114: 77-8.
http://dx.doi.org/10.1016/j.pediatrneurol.2020.10.005
PMID: 33246133

[58] Ninan S, Thompson P, Gershon T, Ford N, Mills W, Jewells V. Fatal pediatric COVID-19 case with seizures and fulminant cerebral edema. Child Neurol Open 2021; 8: 2329048X211022532.
http://dx.doi.org/10.1177/2329048X211022532

[59] Hon KLE, Tsang YCK, Chan LCN, *et al.* Outcome of encephalitis in pediatric intensive care unit. Indian J Pediatr 2016; 83(10): 1098-103.
http://dx.doi.org/10.1007/s12098-016-2068-4 PMID: 27053179

[60] Au CC, Hon KL, Leung AKC, Torres AR. Childhood infectious encephalitis: An overview of clinical features, investigations, treatment, and recent patents. Recent Pat Inflamm Allergy Drug Discov 2021; 14(2): 156-65.
http://dx.doi.org/10.2174/1872213X14999201124195724
PMID: 33238854

[61] Rismanchi N, Gold JJ, Sattar S, *et al.* Neurological outcomes after presumed childhood encephalitis. Pediatr Neurol 2015; 53(3): 200-6.
http://dx.doi.org/10.1016/j.pediatrneurol.2015.05.017
PMID: 26220354

[62] Morishima T, Togashi T, Yokota S, *et al.* Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 2002; 35(5): 512-7.
http://dx.doi.org/10.1086/341407 PMID: 12173123

[63] Leung KKY, Hon KL. Lessons from animal culling during human pandemics: Is vaccination a viable option for animals? Curr Pediatr Rev 2023; 19(1): 2-4.
http://dx.doi.org/10.2174/1573396318666220316124155
PMID: 35297351

[64] Leung TF, Chan PK, Hon KL, Li AM. Surveillance of human- and swine-origin influenza in Hong Kong children. Hong Kong Med J 2018; 24(5)(Suppl. 6): 16-8.
PMID: 30229730

[65] Hon KL, Leung KKY, Tang JW, Leung AKC, Li Y. COVID-19 in Hong Kong – Public health, food safety, and animal vectors perspectives. J Virol Methods 2021; 290: 114036.
http://dx.doi.org/10.1016/j.jviromet.2020.114036 PMID: 33285191

[66] Smith C, Odd D, Harwood R, *et al.* Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. Nat Med 2022; 28(1): 185-92.
http://dx.doi.org/10.1038/s41591-021-01578-1 PMID: 34764489

[67] LaRovere KL, Riggs BJ, Poussaint TY, *et al.* Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol 2021; 78(5): 536-47.
http://dx.doi.org/10.1001/jamaneurol.2021.0504 PMID: 33666649