



**TABLE 1. Associated Neurologic Manifestations of Severe Viral Respiratory Infections**

Respiratory Viral Pathogens	Associated Neurologic Manifestations
Human coronavirus (human variants coronavirus A/B, SARS, Middle Eastern respiratory syndrome, SARS coronavirus 2)	Encephalitis
	Seizures
	Refractory status epilepticus
	ADEM
	GBS
	Leukoencephalopathy
	Critical illness neuromyopathy
Influenza virus (flu A, flu B, H1N1, H5N1)	Febrile seizures
	Acute necrotizing encephalitis
	Encephalitis/encephalopathy
	Reye's syndrome
	ADEM
	GBS
	Seizures
	Myelitis
	Mutism
Parkinsonian symptoms	
Respiratory syncytial virus/orthopneumovirus	Encephalitis
	Seizures
	Status epilepticus
	Central apnea
Human metapneumovirus	Encephalitis
	Focal seizures
	Status epilepticus
Enterovirus (D68, D71)	Acute flaccid myelitis
	Aseptic meningitis
	Viral encephalitis

ADEM = acute disseminated encephalomyelitis, GBS = Guillain-Barré syndrome, SARS = severe acute respiratory syndrome.

invasion of either host cells or phagocytic macrophages to overcome the BBB or the blood-cerebrospinal fluid (CSF) barrier, whereas paracellular migration occurs with pathogen invasion of BBB tight junctions (10). Axonal transport of viral pathogens can occur via sensory, motor, or olfactory nerves. Axonal transport occurs via adherence of motor proteins responsible for retrograde neuronal transport in the periphery as well as in the olfactory nerve which has direct communication with the nasal endothelium where respiratory viral pathogens preferably infect (11). Although each individual virus may have its own predilection for neuroinvasion, there is likely a combination or

additive pathognomonic mode of transmission that occurs during viremia (12).

## CORONAVIRUS

Coronaviridae are a family of RNA viruses that were first isolated in the 1960s from patients with upper respiratory symptoms (13). The virus infects both birds and mammals. Human variants of coronavirus (HCoV) isolated as alphacoronavirus and betacoronavirus are endemic worldwide and generally produce the classical symptoms of HCoV including rhinitis, pharyngitis, laryngitis, bronchitis, and otitis (14). In 2002, a novel coronavirus identified as SARS Co-V was isolated, propagated by zoonotic transmission from bats through and intermediate reservoir (15). Unlike typical HCoV, SARS Co-V was extremely virulent and complicated by high rates of ARDS, multiple organ dysfunction syndrome, and mortality in up to 10% of cases (16, 17). In 2012, a second novel coronavirus, MERS Co-V evolved from zoonotic transmission causing severe respiratory symptoms with a mortality rate of 35% (18). In 2019, a third novel coronavirus, SARS Co-V2, has emerged. This virus has rapidly disseminated to become a pandemic outbreak in early 2020. It shares highly homologous sequence with SARS Co-V and causes acute, highly lethal pneumonia (COVID-19) with clinical symptoms similar to that reported for SARS Co-V and MERS Co-V (19). One difference is that upper respiratory tract signs and symptoms are rare, indicating that the target cells of SARS CoV-2 may be located in the lower airway (20).

The innate virility of Co-V has tropism for both the respiratory tract and the CNS. The neuroinvasive and neurotropic potential of the virus has been well described in studies isolating viral RNA in brain parenchyma outside the blood vessels and is accepted as a vector leading to acute or chronic neurologic disease (5, 21). Viral particles are almost exclusively discovered in neuronal cells, and hematologic or lymphatic routes of viral dissemination are postulated in addition to direct invasion of peripheral nerve terminals and subsequent trans-synaptic transfer (21–23). For acute neurologic disease, the neuropathogenicity of Co-V has been described with associated cases of encephalitis, refractory status epilepticus, GBS, and ADEM during active infection with confirmatory CSF results (24–28). In addition to acute virulence, chronic and persistent infection of human oligodendrocytes and glial cells by Co-V has been demonstrated and proposed to be involved in neuropathologic changes (29, 30). Specifically, an association with development of multiple sclerosis or other demyelinating diseases has been posed (5). Similarly, several acute neurologic manifestations have been reported for SARS Co-V and MERS Co-V, including critical illness neuromyopathy, considered secondary to direct nerve invasion, ADEM, and leukoencephalopathy (31, 32). To date, no rigorous evidence exists describing neurologic involvement of the novel SARS Co-V2. Extrapolating knowledge of neuroinvasion from Co-V in general, it has been proposed that SARS Co-V's neurotropism may play a role in the severe respiratory symptoms, by invasion of medullary neurons and interference with functions of nucleus ambiguus and nucleus tractus solitarius, potentially causing central apnea, and lack of feedback from lung

and respiratory tract receptors (19). Furthermore, headaches were reported by 8% in one of the published series from China (19). In a retrospective case series (not yet peer reviewed) of patients hospitalized with COVID-19 in Wuhan, China, the authors describe that of 214 cases, 36% had neurologic manifestations, with higher prevalence in more severe cases (33). CNS symptoms were present in 25%, with dizziness and headache being the most common, whereas peripheral neuromuscular symptoms were present in 19%. Severe manifestations with impaired consciousness or cerebrovascular disease was also reported, but much less common (33). Acute management strategies for such presentations should be individualized for each underlying manifestation, but overall remains largely supportive and symptomatic. Several drugs have been proposed to be repurposed for the new coronavirus (34). Effectiveness of corticosteroids remains unclear and likely dependent on the phase of illness during which steroids are given (35). Currently, several medications are being investigated for their efficacy and safety for COVID-19 pneumonia, including complement mediators and nucleotide analogues (36), but no specific treatment or prevention of neurologic manifestations exist, other than primary prevention of exposure and infection.

## INFLUENZA

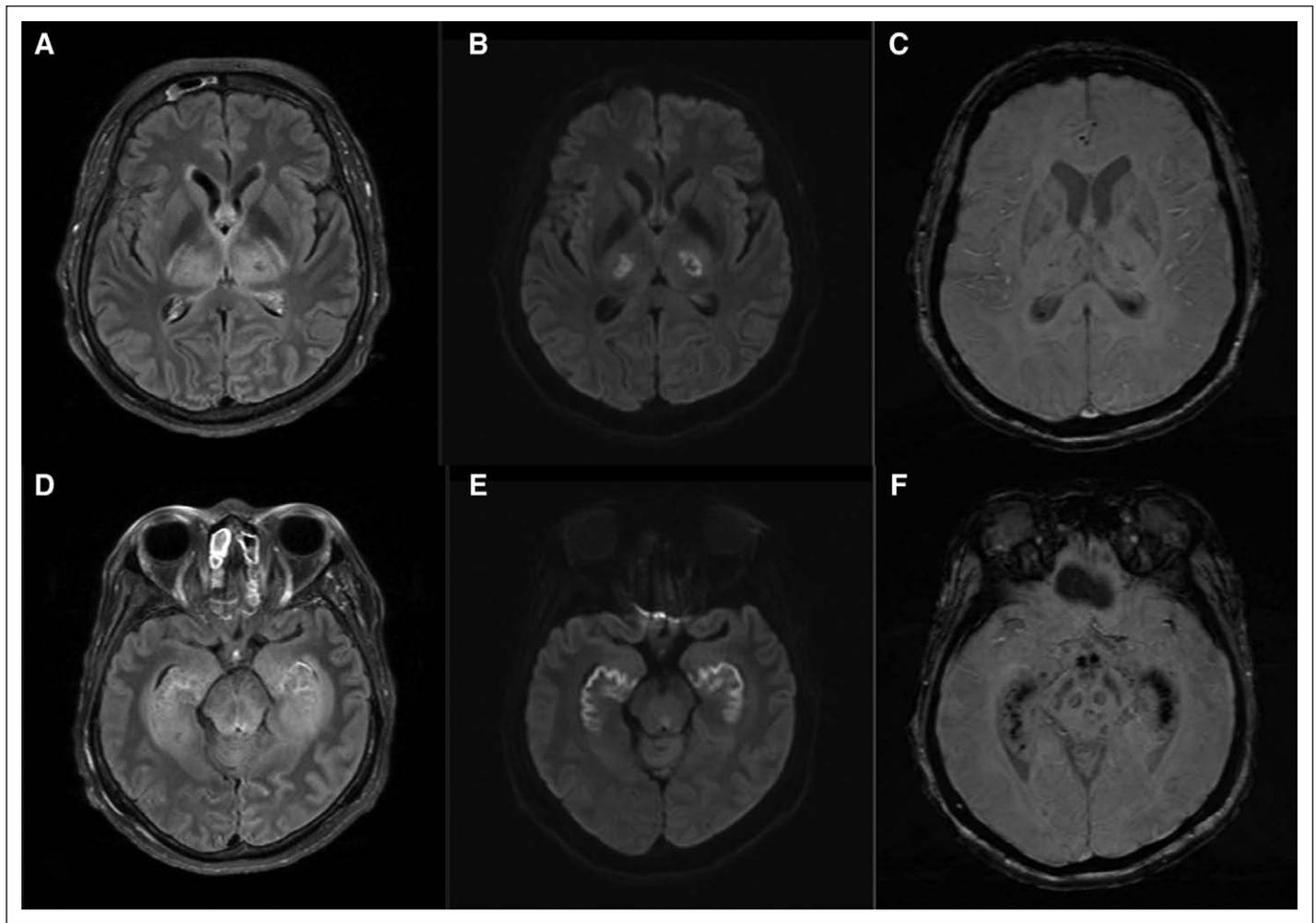
The influenza viruses, formally classified as orthomyxoviridae, are a family of RNA viruses commonly implicated in severe upper respiratory syndromes. There are three genera: influenza virus A, influenza virus B, and influenza virus C, of which, type A is the most virulent human pathogen and causes the most severe form of the disease (37). Diverse phenotypic symptoms are common, from pyrexia, headache, pharyngitis/laryngitis, to ARDS. Influenza infects upwards of 10% of the population annually and has a mortality rate of 4–8.8 deaths per 100,000 persons (38, 39). Individual subtypes of the influenza virus are determined by the structural proteins hemagglutinin (H) and neuraminidase (N). Antigenic shifts that occur within these proteins during zoonotic transmission have led to several pandemics including H1N1 and H5N1 (40, 41). Phenotypic expression within these subtypes tends to be more severe with higher rates of severe lower respiratory infection, ARDS, and death. In addition to the classical respiratory symptoms associated with influenza, a variety of extrapulmonary complications including neurologic, cardiovascular, ocular, hematologic, renal, and hepatic can occur (42).

The neurologic manifestations of influenza have been extensively described (43), vary widely, and have important clinical and prognostic implications. Although generally more prevalent in children, encephalitis, GBS, ADEM, Reye's syndrome, seizures, myelitis, mutism, and Parkinsonian symptoms have been reported in both adult and pediatric populations (42). Historically, febrile seizure is the most frequently encountered influenza-associated CNS complication, with one in five children hospitalized with influenza affected (44). Thirty percent of pediatric deaths related to H1N1 in the United Kingdom presented with encephalopathy and seizures, and neurologic sequelae are among the most severe consequences of the pandemic influenza A H1N1 in survivors (45). The epidemic influenza A (H3N2) strain was associated with a surge in cases of encephalitis/encephalopathy in Japan, Europe,

and the United States (43). One of the best characterized and severe neurologic complications of influenza viremia is acute necrotizing encephalopathy (ANE). Although originally described in the pediatric population, ANE also can affect adults and presents with rapid deterioration in consciousness, symmetric bithalamic, cortical, or infratentorial lesions on MRI and often absence of CSF pleocytosis (see case example in Fig. 1) (46–50). Presence of hemorrhage and tissue loss on imaging in conjunction with CSF are poor prognostic indicators (51). Secondary complications include seizures and status epilepticus. The mortality rate of ANE is upwards of 30% with a significant proportion of patients having long-term neurologic sequelae following recovery (52). Progression to brain death is also a documented complication of ANE (53). In a study of influenza A and B strains in Japan, elevated serum aspartate aminotransferase and creatine phosphokinase and thrombocytopenia (<50,000 platelets/ $\mu$ L) appeared to correlate with unfavorable outcome in influenza-associated encephalopathy (54). Another commonly recognized complication of influenza is GBS, a para- or postinfectious demyelinating polyneuropathy resulting in flaccid quadriplegia and cranial nerve deficits (55, 56). In addition to active infection, the influenza vaccine has also been associated with GBS, although a recent large case-series refutes this evidence (57). Reye's syndrome has also been highly implicated as a parainfectious complication of the influenza virus, especially in children (58). Defined as acute encephalopathy and fatty liver infiltration, Reye's patients generally have a poor prognosis with high mortality. Additional but rare neurologic complications resulting from viral infiltration of specific neuronal structures (basal ganglia, hypothalamus, myelinated axons) include Klein-Levin syndrome, Parkinsonism, transverse myelitis, and ADEM (44).

The exact pathogenesis of the neurologic manifestations of influenza are not entirely clear. Data showing ANE but absence of the influenza virus in the CNS have led to conclude that the inflammatory insult outside the CNS is the trigger for ANE (59), whereas others have hypothesized that disruption of the BBB in the presence of systemic hypercytokinemia could be responsible for inducing necrotic brain lesions (44). Historically, occurrence of Parkinsonian symptoms and "encephalitis lethargica" was reported after the 1918 influenza pandemic (60). However, although there was documented presence of influenza A antigens in patients with "encephalitis lethargica" (61), viral RNA could not be detected in brains of postencephalitic Parkinsonian patients, questioning the exact role of the influenza virus in the genesis of Parkinsonism (62), and calling for long-term follow-up studies among survivors of H5N1-infected individuals to further elucidate the possible direct destructive effect of influenza to the neurons of the substantia nigra.

The mainstay of treatment for influenza infection remains supportive. Patients in high-risk groups are recommended to receive antiviral therapy to shorten illness duration and decrease the occurrence of secondary complications (63), but not all data are affirming strong efficacy for complication prevention (64, 65). For ANE, steroids given within 24 hours after the onset were associated with better outcome of children without brainstem lesions (51) in one series. The use of salicylates should be avoided in children and adolescents due to the association with Reye syndrome.



**Figure 1.** MRI of a 56-yr-old female who presented with 2 d of shortness of breath and upper respiratory congestion, followed by onset of rapidly progressive confusion culminating in seizures and then obtundation. She tested positive for influenza A antigen. Cerebrospinal fluid analysis showed a mild pleocytosis of 13 (82% neutrophils), and polymerase chain reaction testing for other viral encephalitides remained negative. She was treated with oseltamivir immediately upon confirmation of positive influenza testing. MRI at admission showed restricted diffusion and susceptibility along with Fluid-attenuated inversion recovery (FLAIR) hyperintensity, without enhancement, in bilateral thalami (**A–C**) and bilateral mesial temporal lobes (**D–F**) (A+D, FLAIR, B+E, diffusion weighted imaging, C+F, susceptibility weighted imaging sequences).

## RESPIRATORY SYNCYTIAL VIRUS

Human RSV is an RNA virus of the pneumoviridae family. Accordingly, the virus has been renamed orthopneumovirus, but for the clinical context of this article, we will use “RSV” (66). Bronchiolitis, pneumonia, and bronchopneumonia from RSV largely infects the pediatric population and is responsible for a majority of PICU admissions related to pulmonary disease (67). Immunocompromised individuals are also susceptible to infection, and emerging literature suggests a large infection burden within adult populations (68). Extrapulmonary manifestations of RSV are well reported and organ systems typically involved include neurologic, cardiovascular, and hepatic (69).

Neurologic manifestations of acute RSV infection include encephalitis, seizures, status epilepticus, and central apnea and are reported in up to 39% of patients (70, 71). Application of very stringent criteria for diagnosis of neurologic disease in the largest available series yielded, however, only a prevalence of 1.2% (71). Seizure frequency among pediatric patients with RSV was 6.6% in one of the pediatric series (70) but only made for 0.7% of all

patients and represented the majority of neurologic manifestations in other large series (6, 71). Another important neurologic complication following RSV infection is central apnea, which is found in 16%–21% of patients admitted to the ICU (72). Central apnea at admission is a strong predictor for recurrent apneic events and clinical predictor for mechanical ventilation (72). Studies have shown an abnormal laryngeal chemoreflex in patients infected with RSV, implicating CNS pathology as a culprit (73). The exact mechanism of CNS penetration and pathologic response of RSV are unknown; however, CSF samples were positive for the virus in 50% of patients with seizures in the above series (70). With reference to the adult population, scant evidence exists in the literature implicating RSV as a neuropathogen. Treatment for the neurologic sequelae of RSV is generally supportive and symptomatic.

## HUMAN METAPNEUMOVIRUS

Human metapneumovirus (hMPV) is an RNA virus of the paramyxovirus family responsible for upper respiratory infection in all age groups, with more severe infections such as bronchiolitis

and pneumonia affecting the pediatric and immunocompromised populations (74). Since its discovery in 2001, extrapulmonary neurologic manifestations of hMPV have been reported including encephalitis, focal seizures, and status epilepticus or even severe fatal encephalitis mostly in the pediatric but also in the adult population (75–77). The overall prevalence of neurologic complications seems rare, with exact prevalence unknown and most data coming from small case series or single case reports (75). Among 205 pediatric patients referred to the California encephalitis project between 2004 and 2006, hMPV was detected in nasopharyngeal swabs of five patients (6). Compared with infection with RSV, the frequency of seizures is reported to be higher (6.3% vs 0.7%) (6). In a literature review of pediatric cases of hMPV infection complicated by encephalitis, seizures occurred in 10 of 13 cases (75). Infection likely occurs due to direct CNS invasion, as hMPV has been found in brain tissue after autopsy (78). MRI findings can range from normal parenchymal structures to having various degrees of white matter involvement. CSF analysis can range from normal to showing varying degrees of pleocytosis and inconsistent polymerase chain reaction positivity (6). Treatment for the secondary neurologic complications of hMPV remains largely supportive.

## ENTEROVIRUS D68 AND 71

Enteroviruses (EV) D68 and 71 (EV68, EV71) are RNA viruses belonging to the picornaviridae family. Initially discovered in 1968, EV68 was described as a nonpolio enterovirus that infected the upper respiratory tract (79). Isolated in 1969, EV71 was a novel enterovirus found causes hand foot and mouth syndrome (80). A majority of the enterovirus family cause mild symptoms; however, certain strains with specific neurotropism such as EV68 and EV71 have been implicated in severe secondary neurologic sequelae of infection (80–82). EV71 specifically has been demonstrated to cause both aseptic meningitis and viral encephalitis (83, 84). More notably, however, are the recent spikes in cases of acute flaccid paralysis or acute flaccid myelitis (AFM) affecting the pediatric population worldwide (85). Both EV68 and EV71 can result in nonpolio enterovirus paralysis, with EV68 being causative during the most recent outbreak (82, 86, 87). A diagnostic classification for AFM has been proposed for epidemiologic purposes and describes the condition as the acute onset of flaccid paralysis with neuroimaging evidence of spinal cord grey matter lesions (85, 88). High levels of CSF EV-specific antibodies are frequently identified in AFM cases, providing evidence for a causal role of nonpolio EV in AFM (89). Treatment is usually supportive and rehabilitative with outcomes varying from complete clinical recovery to those having persistent residual neurologic deficits (85) and slow recovery (90).

## OTHER COMMON RESPIRATORY VIRUSES

Several other well-known respiratory viruses including rhinovirus, adenovirus, and parainfluenza virus commonly infect the general population. The respiratory symptoms related to infection are generally mild and include upper respiratory manifestations including rhinitis, pharyngitis, and tonsillitis. Although usually self-limited, mild neurologic sequelae including aseptic meningitis, encephalopathy, and febrile seizures have been associated in

up to 3% of patients with such infections (91–95). Aseptic or viral meningitis specifically can have varying clinical presentations ranging from fatigue or headache to alterations in consciousness and seizures (96). CSF analysis typically shows a lymphocytic pleocytosis with hyperproteinemia, although patients can present with normal CSF findings (96, 97). Neurologic symptoms with such viruses tend to be mild, improve with supportive care, and have low-cause morbidity and mortality (95, 98).

## CONCLUSIONS

The neurologic manifestations of severe respiratory viruses including Co-V, influenza, RSV, hMPV, and enterovirus D68 and D71 are a diagnostic and therapeutic challenge for many physicians. Clinical syndromes including status epilepticus, encephalitis, critical illness neuromyopathy, ADEM, ANE, GBS, transverse myelitis, and flaccid paralysis have all been associated with these viral respiratory infections. Having an understanding of the direct neurotropism of such viruses is imperative to understanding pathogenesis, clinical presentation and potential treatment paradigms aimed at improving morbidity and mortality.

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Dr. Robinson has received honoraria for serving as an expert legal witness for traumatic brain injury. Dr. Busl disclosed that she does not have potential conflicts of interest.

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