Letter: Neurological Implications of COVID-19 and Lessons Learned From Prior Epidemics and Pandemics

To the Editor:

We performed a literature review on viral epidemics and pandemics, including the severe acute respiratory syndrome (SARS), the Middle East respiratory syndrome (MERS), influenza H1N1, and the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the goal of identifying the neurological symptoms, signs, and complications of these infections within the context of the COVID-19 pandemic (Figure).

Of 16 articles that included 8042 patients with H1N1, neurological involvement was reported in 1286 patients (15.99%). Excluding headaches, 771 patients had neurological involvement (9.6%) (Table 1). Of 8 articles consisting of 1128 patients with MERS, 323 patients (28.6%) had neurological findings and 170 patients (15.07%) without headache. Of 5 articles with 1251 patients with SARS, 187 patients (14.95%) were reported to have neurological involvement and 6.2% (n = 78) with the exclusion of headache. Of 17 articles on 5335 patients with COVID-19, 744 patients were reported to have neurological signs, symptoms, or sequelae (13.9%) to date, with a rate of 2.47% when headache was excluded (n = 132) (Table 2).

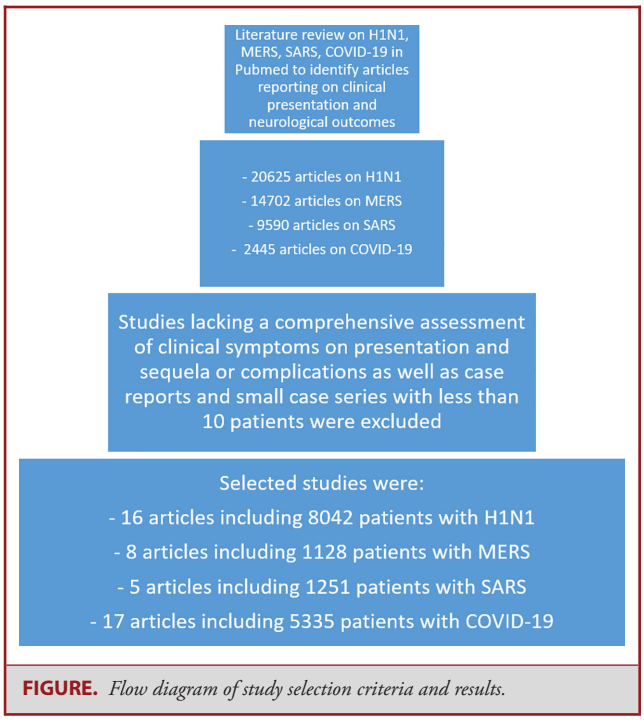

FIGURE. *Flow diagram of study selection criteria and results.*

At this time, the neurological complications of COVID-19 are not fully understood, but reports of prominent neurological symptoms and complications are beginning to emerge.[1] The current incidence of neurological findings with COVID-19 is relatively low, but as data from prior epidemics show, particularly prior coronavirus-related epidemics, the rate is likely to further increase. Neurological manifestations, including headache, dizziness, altered level of consciousness, focal neurological deficits, cranial nerve involvement,[2] seizures, and to a lesser extent meningoencephalitis,[3] more severe necrotizing encephalopathy,[4] cerebral edema, and stroke,[5] have been reported with the recent viral epidemics. Importantly, with prior epidemics (Table 3), there are also several reports of patients developing neurological sequelae months to weeks later, including cerebellitis,[6,7] neuropathy,[8] Guillain-Barré syndrome,[9] postinfluenza myositis,[10] and postviral Parkinsonism.[11]

Coronaviruses are thought to disseminate to the central nervous system (CNS) through either hematogenous spread, retrograde neuronal dissemination, or direct invasion of the olfactory epithelium.[12]

Furthermore, the ACE2 receptor, which is present in the nervous system and the skeletal system,[13] was identified as the functional receptor for SARS-CoV-2.[14] There is also some speculation that invasion into the CNS and damage to the medullary cardiorespiratory centers may lead to worsening respiratory symptoms.[15] Also, with the prior SARS epidemic, multiple human brain specimens demonstrated direct infection of neuronal cells within the cerebral cortex and hypothalamus.[16]

Additionally, there are reports of a hypercoagulable state in certain cases of COVID-19, placing patients at a higher risk of stroke, especially in the setting of acute illness and in the elderly population.[17]

Given the higher prevalence of neurological sequelae reported with prior coronavirus-related pandemics, COVID-19 has the potential of leading to similar if not worse neurological sequelae due to its enhanced virulence. Neurological sequelae can lead to significant morbidity and mortality within survivors, and a heightened attention to neurological findings is required in the ensuing weeks to months.

In conclusion, with the continuing spread of COVID-19 throughout the world and from what the experience from prior epidemics has shown us, neurological findings are likely to increase; therefore, continued monitoring and early recognition is imperative.

TABLE 1. Summary of Literature Review[a]

Study and year	Number of patients	Summary of neurological findings
H1N1		
Wilking et al, 2014[18]	365	Seizure: 17, encephalitis: 4, meningitis: 4, encephalopathy: 3, meningismus: 3, focal hemorrhagic brain lesions: 2, brain infarction: 1, sensorineural hearing loss: 1
Frobert et al, 2011[19]	181	Seizure: 8, encephalitis: 2, encephalopathy: 1, basilar artery thrombosis: 1, myasthenic crisis: 1, decreased consciousness: 1
Ekstrand et al, 2010[20]	303	Seizure: 12, status epilepticus: 7, encephalopathy: 9, headache: 3, focal neurological findings: 5, myositis: 1, aphasia: 6
Glaser et al, 2012[21]	2069	Encephalopathy/encephalitis: 29, seizure: 44, meningitis: 3, Guillain-Barré syndrome: 1
Jain et al, 2009[22]	272	Headache: 92
Tokuhira et al, 2012[23]	81	Seizure: 19, encephalopathy: 14, neurologic long-term complications: 5
Dominguez-Cherit et al, 2009[24]	58	Weakness: 41, headache: 33
Kumar et al, 2009[25]	168	Altered level of consciousness: 17
Archer et al, 2009[26]	100	Headache: 62
Kwon et al, 2012[27]	1389	Seizures: 22, meningitis: 1, encephalopathy: 2
Cao et al, 2009[28]	426	Headache: 83
Libster et al, 2010[29]	251	Headache: 6, seizures: 3
Louie et al, 2009[30]	1088	Headache: 211, altered mental status: 60
Kedia et al, 2011[31]	307	Seizure: 17, encephalopathy: 7
Stein et al, 2010[32]	478	Headache: 51, seizure: 41, meningitis or encephalitis: 5
Khandaker et al, 2012[33]	506	Seizure: 38, encephalitis/encephalopathy 5, confusion/disorientation: 5, loss of consciousness: 5, paralysis/Guillain-Barré syndrome: 2.
MERS		
Arabi et al, 2014[34]	12	Headache: 2, altered consciousness: 1
Noorwali et al, 2015[35]	261	Headache: 59, altered consciousness: 53, focal neurological deficit: 10
Saad et al, 2014[36]	70	Confusion: 18, headache: 9, seizure: 6
Arabi et al, 2017[37]	330	Altered consciousness: 70, headache: 34
Choi et al, 2016[38]	186	Headache: 38, altered consciousness: 10
Assiri et al, 2013[39]	47	Headache: 6
Shalhoub et al, 2018[40]	32	Altered consciousness: 2, headache: 5
Aleanizy et al, 2017[41]	190	No neurological symptoms or complications reported
SARS		
Choi et al, 2003[42]	267	Headache: 89, dizziness: 48, confusion: 2
Umapathi et al, 2004[5]	206	Large artery cerebral infarctions: 5
Tsai et al, 2005[43]	664	Polyneuropathy: 3, large artery ischemic stroke: 5
Leung and Chiu, 2004[44]	64	Headache: 18, dizziness: 12, altered consciousness: 3
Lien et al, 2008[45]	50	Headache: 2
COVID-19		
Mao et al, 2020[46]	214	Dizziness: 36, headache: 28, altered consciousness: 16, acute cerebrovascular disease: 6, ataxia: 1, seizure: 1, hypogeusia: 12, hyposmia: 11, hypopsia: 3, neuralgia: 5
Xu et al, 2020[47]	62	Headache: 21
Chen et al, 2020[48]	274	Headache: 3, dizziness: 21, altered consciousness: 26
Wu et al, 2020[49]	80	Headache: 13
Lian et al, 2020[50]	788	Headache: 75
Wang et al, 2020[51]	69	Headache: 10, dizziness: 5
Guan et al, 2020[52]	1590	Headache: 205, altered consciousness: 20
Arentz et al, 2020[53]	21	Seizure: 1
Wan et al, 2020[54]	135	Headache: 24
Chu et al, 2020[55]	54	Unspecified
Huang et al, 2020[56]	34	Headache: 2
Yang et al, 2020[57]	149	Headache: 13
Yang et al, 2002[58]	52	Headache: 3
Guan et al, 2020[59]	1099	Headache: 150
Korea Centers for Disease Control and Prevention[60]	28	Headache: 3
Huang et al, 2020[61]	41	Headache: 3
Zheng et al, 2020[62]	645	Headache: 67

[a] All studies were retrospective, except Howlett et al, 2018, which was prospective.

TABLE 2. Neurologic Complications by Viral Disease

Neurologic finding	Number of patients	Percent
H1N1		
Headache	541	6.73%
Seizure	228	2.84%
Encephalitis/encephalopathy (often grouped together)	76	0.95%
Weakness	41	0.51%
Altered level of consciousness	22	0.27%
Meningitis	13	0.16%
Speech difficulties	6	0.07%
Cognitive and memory issues	5	0.06%
Cranial nerve or focal deficit	5	0.06%
Neurological long-term complications, not specified	5	0.06%
Stroke	4	0.05%
Guillain-Barré syndrome	3	0.04%
Hearing impairment and tinnitus	1	0.01%
MERS		
Headache	147	13.03%
Altered level of consciousness	136	12.06%
Cognitive or memory issues	18	1.60%
Cranial nerve or focal deficit	10	0.89%
Seizure	6	0.53%
SARS		
Headache	109	8.71%
Dizziness	60	4.80%
Stroke	10	0.80%
Altered level of consciousness	5	0.40%
Neuropathy	3	0.24%
COVID-19		
Headache	620	11.74%
Dizziness	62	1.17%
Altered level of consciousness	62	1.17%
Diminished taste sensation	12	0.23%
Diminished smell	11	0.21%
Stroke	6	0.11%
Neuralgia	5	0.09%
Seizure	2	0.04%
Ataxia	1	0.02%

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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TABLE 3. Year Identified, Total Case Numbers, and Case Fatality Rates of SARS, H1N1, MERS, and COVID-19

Virus	Year identified	Number of countries affected	Number of cases	Number of deaths	Case fatality rate
H1N1	2009	>214	0.7 to 1.4 billion	18 036 (confirmed) 284 000 (estimated)	0.03% (estimated)
SARS (SARS-CoV)	2002	26	8437	813	9.6%
MERS	2012	27	2499	861	34.5%
COVID-19	2019	>205	>2 million	33 509	4.8%

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