What did we learn from the previous coronavirus epidemics and what can we do better: a neuroinfectiological point of view

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To the Editor

We are learning gradually about the neurological manifestations during the ongoing coronavirus disease (COVID-19) pandemic, a respiratory disease related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. As the clinical evidence is still limited, it makes sense to critically analyze the spectrum of neurological involvement caused by SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), which were causal for epidemics in 2003 and 2012, respectively.

Coronaviruses belong to a family of enveloped, single-stranded RNA viruses which have the ability to cross the species barrier to infect humans and other animals [2]. The first detection of coronaviruses in the human central nervous system dates back to 1980, when the virus was isolated on brain autopsy in two patients with multiple sclerosis [3]. In the meantime, we have learned that SARS-CoV-2 is the seventh coronavirus known to infect humans, and bats and pangolins could be the natural reservoirs and intermediate animal species [2]. MERS-CoV is capable of infecting human neuronal cells *in vitro* but its receptor dipeptidyl peptidase 4 has a low expression in the brain [4]. So far, this virus has not been isolated in the neural tissues or cerebrospinal fluid (CSF) of affected human beings. In contrast, several routes of central nervous system entry and infection of neurons have been reported in experimental animal models for SARS-CoV-1, which shares the receptor for cell entry with SARS-CoV-2 but binds with a 10–20-fold lower affinity [4].

Here, we performed a systematic analysis of available evidence of neurological manifestation during the respective outbreaks using appropriate search criteria; the findings are shown in Table 1.

A systematic review was carried out to study cases reporting nervous system involvement in patients with SARS-CoV-1 and MERS-CoV infection. We searched PubMed and Google Scholar databases for papers published from 1 January 2003 to 1 January 2020 regarding nervous system and SARS-CoV-1 or nervous system and MERS-CoV. The search strings for PubMed were as follows: ((‘SARS-CoV1’ [all fields] OR ‘SARS’ [all fields] OR ‘MERS-CoV’ [all fields] OR ‘MERS’ [all fields]) AND ((‘neurology’ [MeSH terms] OR ‘neurolog*’ [all fields]) OR (‘brain’ [MeSH terms] OR ‘brain’ [all fields]) OR (‘neuro’ [all fields]) OR (‘meningitis’ [MeSH terms] OR ‘meningitis’ [all fields]) OR (‘encephalitis’ [MeSH terms] OR ‘encephalitis’ [all fields]) OR (‘PNS’ [MeSH terms] OR ‘PNS’ [all fields]) AND (‘2003/01/01’ [PDAT]: ‘2020/01/01’ [PDAT])). We also hand-searched reference lists of all articles identified in the electronic search using common search engines (e.g. Google, Bing).

SARS-CoV-1

Hung *et al.* reported the first case of SARS-CoV-1 infection with neurological manifestations in a 59-year-old woman during the pandemic [5]. In addition to respiratory symptoms, she developed generalized seizures and SARS-CoV-1 was confirmed in CSF by polymerase chain reaction (PCR). Lau *et al.* described the case of a 34-year-old woman in week 26 of pregnancy at the time of acute respiratory symptoms [6]. She required mechanical ventilation on day 7, was treated for acute renal failure on day 8 and had generalized tonic–clonic seizures on day 22. PCR for SARS-CoV-1 was positive in the CSF. In a study conducted by Li *et al.*, a total of 183 hospitalized children with respiratory tract infection acute encephalitis-like syndrome were screened for anti-SARS-CoV-1 immunoglobulin M antibodies [7]. 22/183 (12%) patients were seropositive; in this subgroup pleocytosis and elevated CSF protein were found in 10 (46%) and six (36%) patients, respectively. PCR examination of CSF was not performed; full recovery was seen all patients.

Tsai *et al.* reviewed 664 probable SARS-CoV-1 infections in Taiwan. Three patients in this cohort developed axonopathic polyneuropathy 3–4 weeks after the onset of SARS; two SARS patients have experienced myopathy. All these neuromuscular disorders were evaluated as critical illness neuropathy and myopathy [8,9].

A group from Singapore reported five cases of large artery cerebral infarctions among 206 patients with SARS-CoV-1. Two of them remained critically ill and three died. Significant hypotension was present just before the onset of stroke in four patients [10].

Table 1 Patients with neurological complications associated with SARS- and MERS-CoV infection

Condition	Reference	Country	*N*	Age/sex	Neurological diagnosis	Comorbidities	CSF analysis	Outcome
SARS-CoV-1	Lau *et al.* (2004) [6]	Hong Kong, China	1	32F	Generalized tonic–clonic convulsion	None; 26 weeks in pregnancy	Elevated protein, positive RT-PCR for SARS-CoV-1	Recovered
SARS-CoV-1	Hung *et al.* (2003) [5]	Hong Kong, China	1	59F	Generalized tonic–clonic seizures	None	Positive RT-PCR for SARS-CoV-1; otherwise normal	Recovered
SARS-CoV-1	Tsai *et al.* (2005) [13]	Taiwan	4	51F 48F 42F* 31M	Patient 1 – sensorimotor polyneuropathy Patient 2 – sensorimotor polyneuropathy Patient 3 – sensorimotor polyneuropathy and myopathy Patient 4 – myopathy	None	Not done; elevated protein; elevated protein; not done	Improved or recovered
SARS-CoV-1	Umapathi *et al.* (2004) [9]	Singapore	5	68F 64F 54F 63F 39F	Large artery ischaemic stroke in all patients	None; none; dyslipidaemia; diabetes mellitus and hypertension; none	Not done	Critically ill; died; died; critically ill; died
MERS-CoV	Algahtani *et al.* (2016) [10]	Saudi Arabia	2	34/F 28/M	Intracerebral hemorrhage, critical illness polyneuropathy	Diabetes mellitus; none	Not done; normal, negative for MERS-CoV-1	Died; recovered
MERS-CoV	Arabi *et al.* (2015) [11]	Saudi Arabia	3	74/M 57/M 45/M	ADEM, bilateral anterior cerebral artery stroke, encephalitis	Diabetes mellitus, hypertension in all three cases	Negative for MERS-CoV, elevated protein; CSF not taken; negative for MERS-CoV, elevated protein	Died;died; recovered
MERS-CoV	Kim *et al.* (2017) [12]	Republic of Korea	4	55/M 43/F 46/M 38/F	Patient 1 – Bickerstaff encephalitis and overlap with GBS Patient 2 – critical illness polyneuropathy or GBS Patient 3 – infectious or toxic polyneuropathy Patient 4 – infectious or toxic neuropathy	Atrial fibrillation, diabetes mellitus, hypertension, chronic kidney disease, hypothyroidism; none; hypertension and a history of pulmonary tuberculosis; none	Normal, negative for MERS-CoV; not collected in the other three patients	All patientsrecovered

ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; F, female; GBS, Guillain–Barré syndrome; M, male; MERS-CoV, Middle East respiratory syndrome coronavirus; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-1, severe acute respiratory syndrome coronavirus 1. Tracheal aspirate, sputum or serum PCR were positive for CoV in most of the patients. *This patient was not positive for CoV-1 by PCR. The serum serology test was positive.

Table 2 Potential indications for CSF tap in COVID-19 positive patients with new neurological signs and symptoms during or shortly after COVID-19

Condition	Signs and symptoms/underlying disorders
Signs of (meningo-)encephalitis of no plausible differential etiology or no better explanation	For case definition, see [16]
Focal neurological deficit of no plausible differential etiology/no better explanation	Specifically• acute anosmia • acute/subacute cranial (poly-)neuropathies • acute/subacute brain stem disorders • subacute neuralgias • subacute ascending paresis (GBS-like) • subacute myopathy • pathological breathing pattern
Delirious condition of no plausible differential etiology or no better explanation	E.g. delirium of unclear etiology, i.e. without hypoxia, no high fever
Convulsive or non-convulsive seizures of no plausible differential etiology or no better explanation	For case definition, see [12]
Acute cerebrovascular disorders including • ischaemia • intracerebral hemorrhage • subarachnoidal hemorrhage • subdural hematoma • sinus vein thrombosis	• Without disseminated intravasal coagulation • Without primarily COVID-19-associated coagulation disorder • COVID-19-associated vasculitis?
ICU patients with disorders of consciousness of no plausible differential etiology or no better explanation	• Unresponsive wake-up trials • EEG shows signs of unclear encephalopathy • Myoclonia or dyskinesias

CSF, cerebrospinal fluid; EEG, electroencephalography; GBS, Guillain–Barré syndrome, ICU, intensive care unit.

MERS-CoV

MERS-CoV first appeared in September 2012 in Saudi Arabia. By the end of 2019, globally a total of 2494 laboratory-confirmed cases and 858 deaths (34.4%) had been reported by the World Health Organization. Algahtani *et al.* reported two patients with neurological complications within a cohort of 120 confirmed cases of MERS-CoV disease [11]. One patient died from intracerebral hemorrhage, which was the result of thrombocytopenia, disseminated intravascular coagulation and platelet dysfunction. The other patient had critical illness polyneuropathy complicating a stay at the intensive care unit. Another group reported three additional patients with MERS and neurological disorders [12]. These were acute disseminated encephalomyelitis, bilateral anterior circulation ischaemic stroke and encephalitis. Four out of 23 MERS patients in a designated hospital had neurological complications [13]. The diagnoses included Bickerstaff's encephalitis/Guillain–Barré syndrome, intensive-care-unit-acquired weakness, and toxic or infectious neuropathies. The neurological symptoms started 2–3 weeks after the onset of respiratory symptoms. None of the MERS cases had a positive PCR in CSF.

Discussion

The review of available evidence yielded only a limited number of neurological cases. In addition, prospective data collection or epidemiologically relevant analyses were not performed from a neurological point of view. The main finding is the neuroinvasive potential of SARS-CoV-1 with detection of the virus in CSF. Interestingly, cases with typical encephalitic symptoms or corresponding radiological features were not reported. On the other hand, the MERS cases had a time lag from respiratory to neurological symptoms and no detection of virus in CSF, which resembles a parainfectious mechanism. The MERS case with brain hemorrhage could also be of relevance for SARS-CoV-2 patients with coagulation abnormalities.

Neuromuscular disorders in SARS-CoV-1 and MERS patients are usually considered as critical illness neuropathies, but the possibility of direct attack by SARS-CoV-1 on the nervous system could not be excluded. Multiple factors may be contributing to the vascular insult in coronavirus infection, including hypercoagulable status related to coronavirus, septic and cardiogenic shock, and possible vasculitis. The relationship between SARS and MERS and the above neurological problems still needs further clarification [14].

We do see a significant reporting bias and a negligible involvement of neurologists in the previous epidemics. Now, in the wake of COVID-19, we can question what we could do better from a strategic neuroinfectiological viewpoint. We not only want to get insights to the clinical spectrum and course of infectious and parainfectious manifestations from adequately confirmed cases. This can be assured by active involvement of neurologists in the care of COVID-19 patients [15]. Concerted efforts to collect patient data including the EANCore initiative could expand the knowledge about susceptibility, prognostic factors and shortcomings of the current patient care. Key to this goal is standardized reporting as well as diagnostic procedures with state-of-the-art laboratory examination, neuroimaging and exclusion of differentials. In addition, as long as the spectrum neuro-COVID-19 or COVID-19-associated neurological disorders is not well

characterized, a permissive strategy for CSF examination and PCR testing for SARS-CoV-2 seems reasonable. A list of considerations for clinical symptoms and constellations, in which CSF diagnostics in SARS-CoV-2 positive patients could be of relevance, is shown in Table 2. Also, neuropathology and CSF data banking could provide valuable insights to be better prepared for upcoming neuroinfectious challenges.

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