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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 neurologic manifestations during the ongoing coronavirus disease 2019 (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 a sense to critically analyze the spectrum of neurologic 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 (CNS) 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 in-vitro but its receptor dipeptidyl peptidase 4 (DDP4) has a low expression in the brain [4]. So far, this virus has not been isolated in neural tissues or cerebrospinal fluid (CSF) of affected human beings. In contrast, several routes of CNS 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 neurologic 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-CoV1 and MERS-CoV infection. We searched PubMed and Google Scholar databases for papers published from 1st January 2003 to January 1st 2020 regarding nervous system and SARS-CoV1 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 IgM antibodies. 22/183 (12%) patients were seropositive; in this subgroup pleocytosis and elevated CSF protein was found in 10 (46%) and 6 (36%) patients, respectively. PCR examination of CSF was not performed; full recovery was seen in 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 onset of SARS; two SARS patients have experienced myopathy. All these neuromuscular disorders were evaluated as critical illness neuropathy and myopathy [7,8].

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 [9].

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 (WHO). Algattani et al. reported two patients with neurological complications within the cohort of 120 confirmed cases of MERS-CoV disease [10]. One patient died from intracerebral hemorrhage, which was the result of thrombocytopenia, disseminated intravascular coagulation, and platelet dysfunction. The other patient had critical illness polynuropathy complicating a stay at the intensive care unit (ICU). Another group reported three additional patients with MERS and neurologic disorders [11]. These were acute disseminated encephalomyelitis, bilateral anterior circulation ischemic stroke and encephalitis. Four out of 23 MERS patients in a designated hospital had neurologic complications [12]. The diagnoses included Bickerstaff’s encephalitis/Guillain-Barré syndrome, intensive-care-unit-acquired weakness, and toxic or infectious...
neuropathies. The neurologic symptoms started 2–3 weeks after the onset of respiratory symptoms. If investigated, none of the MERS cases had a positive PCR in CSF.

Discussion

The review of available evidence yielded only a limited number of neurologic 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 nerve 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 above neurological problems still needs further clarification [13].

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 [14]. 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 a standardized reporting as well as diagnostic procedures with state-of-the art laboratory exam, 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.
References

[1]. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med. 2020.

[2]. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020 26: 450-452.

[3]. Burks JS, DeVald BL, Jankovsky LD, Gerdes JC. Two coronaviruses isolated from central nervous system tissue of two multiple sclerosis patients. Science. 1980 209: 933-934.

[4]. Natoli S, Oliveire V, Calabresi V, Maia LF, Pisani A. Does SARD-CoV-2 invade the brain? Translational lessons from animal models. Eur J Neurol. 2020 in press.

[5]. Hung EC, Chim SS, Chan PK, et al. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. Clin Chem. 2003 49: 2108-2109.

[6]. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis. 2004 10: 342-344.

[7]. Tsai LK, Hsieh ST, Chao CC, et al. Neuromuscular disorders in severe acute respiratory syndrome. Arch Neurol. 2004;61(11):1669-1673. doi:10.1001/archneur.61.11.1669

[8]. Chao CC, Tsai LK, Chiou YH, et al. Peripheral nerve disease in SARS:: report of a case. Neurology. 2003;61(12):1820-1821. doi:10.1212/01.wnl.0000099171.26943.d0

[9]. Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol. 2004;251(10):1227-1231. doi:10.1007/s00415-004-0519-8

[10]. Algahtani H, Subahi A, Shirah B. Neurological Complications of Middle East Respiratory Syndrome Coronavirus: A Report of Two Cases and Review of the Literature. Case Rep Neurol Med. 2016 2016: 3502683.

[11]. Arabi YM, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection. 2015 43: 495-501.

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[12]. Kim JE, Heo JH, Kim HO, et al. Neurological Complications during Treatment of Middle East Respiratory Syndrome. *J Clin Neurol*. 2017 **13**: 227-233.

[13]. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan*. 2005;14(3):113-119.

[14]. Sellner J, Taba P, Öztürk S, Helbok R. The need for neurologists in the care of COVID-19 patients. *Eur J Neurol*. 2020 Apr 23. doi: 10.1111/ene.14257. Online ahead of print.

[15]. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis*. 2013 **57**: 1114-1128.
Table 1: Patients with neurological complications associated with SARS- and MERS-CoV infection. Tracheal aspirate, sputum or serum PCR were positive for CoV in most of the patients.

| Condition | Reference            | Country        | N= | Age/Sex | Neurologic 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) [12]| 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) [15]| Singapore | 5  | 68F 64F 54F | Large artery ischemic stroke in all patients              | None; none; dyslipidaemia; diabetes mellitus | not done                                  | critically ill; died; died; critically ill, |
| MERS-CoV | Alqahtani et al. (2016) [7] | Saudi Arabia | 2 | 34/F, 28/M | Intracerebral hemorrhage, Critical illness polyneuropathy | #1 – diabetes mellitus; #2 – None | not done; normal, negative for MERS-CoV-1 | died |
|----------|--------------------------|--------------|---|-------------|-------------------------------------------------|--------------------------------|--------------------------------|------|
| MERS-CoV | Arabi et al. (2015) [8]  | 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 | #1 – died; #2 – died; #3 – recovered |
| MERS-CoV | Kim et al. (2017) [9]    | 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 | #1 - atrial fibrillation, diabetes mellitus, hypertension, chronic kidney disease, hypothyroidism #2 – None #3 - hypertension and a history of pulmonary tuberculosis #4 - None | #1 - normal, negative for MERS-CoV; not collected in the other three patients. | All patients – recovered |
*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 [15] |
| 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 |
| Condition                                                                 | Definition                                                                 |
|--------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Delirious condition of no plausible differential etiology or no better   | e.g. delirium of unclear etiology, i.e. without hypoxia, no high fever     |
| explanation                                                              |                                                                           |
| Convulsive or non-convulsive seizures of no plausible differential        | For case definition, see [11]                                             |
| etiology or no better explanation                                         |                                                                           |
| Acute cerebrovascular disorders including                                |                                                                           |
| • ischemia                                                               |                                                                           |
| • intracerebral hemorrhage                                               |                                                                           |
| • subarachnoidal hemorrhage                                              |                                                                           |
| • subdural hematoma                                                      |                                                                           |
| • sinus vein thrombosis                                                  |                                                                           |
| • without disseminated intravascular 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                                               |                                                                           |

Legend: GBS Guillain-Barré syndrome, ICU intensive care unit