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General review

Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: A narrative review for clinicians

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ABSTRACT

Introduction. – The past two decades have been marked by three epidemics linked to emerging coronaviruses. The COVID-19 pandemic highlighted the existence of neurological manifestations associated with SARS-CoV-2 infection and raised the question of the neuropathogenicity of coronaviruses. The aim of this review was to summarize the current data about neurological manifestations and diseases linked to human coronaviruses.

Material and methods. – Articles have been identified by searches of PubMed and Google scholar up to September 25, 2020, using a combination of coronavirus and neurology search terms and adding relevant references in the articles.

Results. – We found five cohorts providing prevalence data of neurological symptoms among a total of 2533 hospitalized COVID-19 patients, and articles focusing on COVID-19 patients with neurological manifestations including a total of 580 patients. Neurological symptoms involved up to 73% of COVID-19 hospitalized patients, and were mostly headache, myalgias and impaired consciousness. Central nervous system (CNS) manifestations reported in COVID-19 were mostly non-specific encephalopathies that represented between 13% and 40% of all neurological manifestations; post-infectious syndromes including acute demyelinating encephalomyelitis (ADEM, $n = 13$), acute necrotizing encephalopathy (ANE, $n = 4$), Bickerstaff's encephalitis ($n = 5$), generalized myoclonus ($n = 3$) and acute transverse myelitis ($n = 7$); other encephalitis including limbic encephalitis ($n = 9$) and miscellaneous encephalitis with variable radiologic findings ($n = 26$); acute cerebrovascular diseases including ischemic strokes (between 1.3% and 4.7% of COVID-19 patients), hemorrhagic strokes ($n = 17$), cerebral venous thrombosis ($n = 8$) and posterior reversible encephalopathy ($n = 5$). Peripheral nervous system (PNS) manifestations reported in COVID-19 were the following: Guillain–Barré syndrome ($n = 31$) and variants including Miller Fisher syndrome ($n = 3$), polyneuritis cranialis ($n = 2$) and facial diplegia ($n = 2$); isolated oculomotor neuropa-

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thy (n = 6); critical illness myopathy (*n* = 6). Neuropathological studies in COVID-19 patients demonstrated different patterns of CNS damage, mostly ischemic and hemorrhagic changes with few cases of inflammatory injuries. Only one case suggested SARS-CoV-2 infiltration in endothelial and neural cells. We found 10 case reports or case series describing 22 patients with neurological manifestations associated with other human coronaviruses. Among them we found four MERS patients with ADEM or Bickerstaff's encephalitis, two SARS patients with encephalitis who had a positive SARS-CoV PCR in cerebrospinal fluid, five patients with ischemic strokes associated with SARS, eight MERS patients with critical illness neuromyopathy and one MERS patient with Guillain–Barré Syndrome. An autopsy study on SARS-CoV patients demonstrated the presence of the virus in the brain of eight patients.

Conclusion. – The wide range of neurological manifestations and diseases associated with SARS-CoV-2 is consistent with multiple pathogenic pathways including post-infectious mechanisms, septic-associated encephalopathies, coagulopathy or endothelitis. There was no definite evidence to support direct neuropathogenicity of SARS-CoV-2.

1. Introduction

The past two decades have been marked by three epidemics linked to emerging coronaviruses, severe acute respiratory syndrome (SARS) in 2002, middle east respiratory syndrome (MERS) in 2012 and the ongoing pandemic of coronavirus disease 2019 (COVID-19). Other human coronaviruses (HCoV) circulate ubiquitously and are responsible for mild upper or lower respiratory tract infections.

The first cases of COVID-19, the disease linked to SARS-CoV-2 were reported in China in December 2019. Since then, the virus has continued to spread and on March 11, 2020 the World Health Organization (WHO) characterized COVID-19 as a pandemic [1]. As of October 3, 2020, more than 34 million cases have been reported worldwide with more than one million deaths. For the majority of the patients, COVID-19 causes fever and respiratory signs related to pneumonia. Less frequent symptoms have been described such as gastrointestinal symptoms, dermatological manifestations, cardiovascular events or neurological manifestations. A first retrospective series on 214 hospitalized patients reported neurological symptoms for 36% of the cases [2]. Other articles and series have since been published with multiple neurological manifestations or characterized neurological diseases, such as Guillain–Barré syndrome or encephalitis, associated with SARS-CoV-2 infection. The objective of this narrative review is to describe the current data about neurological manifestations linked to human coronaviruses in order to provide a useful summary for clinical practice.

2. Material and methods

2.1. Search strategy

Articles for this review have been identified by searches of PubMed up to September 25, 2020. We have been searching for the combination of coronaviruses search terms (Coronaviruses, COVID-19, SARS-CoV-2, SARS-CoV, MERS-CoV, HCoV-OC43) and neurological search terms (neurological symptoms, nervous system, encephalopathy, encephalitis, myelitis, stroke, seizure, epilepsy, neuropathy, Guillain–Barré syndrome). We have also conducted an ''incognito'' Google Scholar search with these search terms to further identify articles related to neurological manifestations of coronaviruses. We then screened the references of all the articles found and added articles relevant to the topic.

2.2. Study selection

Prospective and retrospective articles in English that reported neurological manifestations linked to human coronaviruses have been included. Neurological manifestations have been systematically extracted from the selected articles and analyzed in the review. Regarding COVID-19, we split articles into case series reporting characterized neurological diseases associated with SARS-CoV-2 and large cohorts of hospitalized COVID-19 patients that described general clinical characteristics including neurological manifestations.

3. Results

3.1. Neurological manifestations associated with SARS-CoV-2 infection

To date, five cohort studies provided a prevalence of neurological manifestations in a total of 2533 COVID-19 patients [2–6] (Table 1). This prevalence ranged from 4.3 to 73.0% depending on which symptoms are considered. The most common manifestations were myalgia (1.8 to 32.4%), headache (1.8 to 20.4%), and impaired consciousness (1.8 to 21.3%). Four other cohort studies focused only on COVID-19 patients with neurological manifestations and described 482 patients [7–10] (Table 1). In addition, we identified 57 articles reporting 98 COVID-19 patients with characterized neurological diseases (Table 2).

3.1.1. Encephalitis and encephalopathies

Impaired consciousness was one of the most common neurological symptoms in cohort studies, reported in 1.8 to 21.3% of hospitalized COVID-19 patients [2–6] (Table 1), up to

Table 1 – Prevalence and characteristics of neurological manifestations in COVID-19 patients: data from eight cohort studies.

Authors	Mao et al.	Romero-Sanchez et al.	Mahammedi et al.	Guilmot et al.	Agarwal et al.	Varatharaj et al.	Kremer et al.	Paterson et al.	Meppiel et al.
Setting	China, 3 centers	Spain, 2 centers	Italy, 3 centers	Belgium, 3 centers	USA, 1 center	UK-wide surveillance study	France, 11 centers	UK, 1 center	France, 46 centers
COVID-19 patients, total *n* (%)	214 (100)	841 (100)	725 (100)	349 (100)	404 (100)	–	–	–	–
COVID-19 patients with neurological symptoms, *n* (%)	78 (36.4)	483 (57.4)	108 (14.9)	15 (4.3)	295 (73.0)	153	64	43	222
Headache	28 (13.1)	119 (14.1)	13 (1.8)	–	82 (20.3)	–	10	–	24
Dizziness	36 (16.8)	51 (6.1)	4 (0.6)	–	31 (7.7)	–	–	–	5
Altered mental status and/or impaired consciousness	16 (7.5)	165 (19.6)	64 (8.8)	7 (1.5)	86 (21.3)	39	34	–	117
Ataxia	1 (0.5)	–	2 (0.3)	–	20 (5.0)	–	–	–	–
Seizure	1 (0.5)	6 (0.7)	1 (0.1)	2 (0.6)	2 (0.5)	-	2	1	21
Anosmia	12 (5.6)	41 (4.9)	2 (0.3)	2 (0.6)	18 (4.5)	1	1	-	7
Nerve pain	5 (2.3)	–	3 (0.4)	–		–	–	–	–
Dysautonomia	–	21 (2.5)	–	–	1 (0.2)	–	–	–	–
Neuropsychiatric	–	167 (19.8)	–	3 (0.9)		–	–	–	–
Myalgia	23 (10.7)	145 (17.2)	13 (1.8)	–	131 (32.4)	23	–	–	–
Neurological manifestations, *n* (%)									
Acute cerebrovascular disease	6 (2.8)	14 (1.7)	42 (5.8)	3 (0.9)	3 (0.7)	77	–	–	57
Ischemic stroke	–	11 (1.3)	34 (4.7)	2 (0.6)	2 (0.5)	57	17	8	52
Hemorrhagic stroke	–	–	6 (0.8)	1 (0.3)	1 (0.3)	9	–	–	5
Cerebral Venous Thrombosis	–	–	2 (0.3)	0	0	2	–	–	1
Posterior reversible encephalopathy	–	1 (0.1)	1 (0.1)	0	0	–	–	–	0
Encephalopathy/ encephalitis	–	1 (0.1)	4 (0.6)[a]	10 (2.9)[c]	86 (21.3)	16	19[e]	21[f]	88[g]
Myelitis	–	–	–	–	–	–	–	–	0
Guillain–Barré syndrome and variants	–	1 (0.1)	3 (0.4)[b]	1 (0.3)[d]	0	4	–	7	15[h]
Isolated oculomotor neuropathy	–	–	–	1 (0.3)	0	–	–	1	2

[a] Non-specific encephalopathy (*n* = 3) with ischemic lesions in one; encephalopathy with multifocal areas of cortical FLAIR hyperintensities (*n* = 1)
[b] Guillain–Barré syndrome (*n* = 2); Miller Fisher Syndrome (*n* = 1)
[c] Non-specific encephalopathy (*n* = 6); Bickerstaff brainstem encephalitis (*n* = 2); delirium, akathisia and chorea (*n* = 1); limbic encephalitis (*n* = 1)
[d] Polyneuritis cranialis
[e] Leptomeningeal enhancement (*n* = 11); limbic encephalitis (*n* = 2), ANE (*n* = 2), ADEM (n = 1), cytotoxic lesion in the corpus callosum (n = 1), encephalitis with supratentorial white matter hyperintensities (*n* = 1), encephalitis with middle cerebellar peduncles hyperintensities (*n* = 1)
[f] Non-specific encephalopathy (*n* = 10); ADEM (*n* = 9), brainstem encephalitis (*n* = 1); limbic encephalitis (*n* = 1)
[g] Non-specific encephalopathy (*n* = 67) with microvascular lesions in 8; encephalitis (*n* = 21) with unremarkable MRI (*n* = 6), brainstem encephalitis (*n* = 1), limbic encephalitis (*n* = 3), white matter and/or basal ganglia abnormalities without mention of ADEM or ANE (8), focal leptomeningeal T2 hyperintensity (*n* = 2) cytotoxic lesion in the corpus callosum (*n* = 1)
[h] Guillain–Barré syndrome (*n* = 14), Facial diplegia (*n* = 1).

69% in severe patients needing intensive care management [11]. Disorder of consciousness occurred with a mean time of onset of 8 to 9 days in the evolution of COVID-19, and was associated with severe infection, older age, higher creatine kinase levels, lower lymphocyte counts and higher blood urea nitrogen [2,3]. A diagnosis of encephalopathy or encephalitis was reported in only 0.1 to 3% of patients in these cohort studies. However, among all the neurological manifestations,

Table 2 – Case reports and case series of patients with COVID-19, SRAS, and MERS associated with neurological manifestations (published between March and June 2020).

	SARS-CoV-2 (COVID-19)	SARS-CoV (SARS)	MERS-CoV (MERS)
Number of patients, total N	98 [56 references]	11 [4 references]	11 [6 references]
Patients with CNS manifestations, n/N	69/98 71% [39 references]	7/11 64% [3 references]	6/10 60% [4 references]
Encephalopathy and encephalitis, n/N	14/98 14%	2/11 18%	4/10 40%
References	Bernard-Valnet et al., 2020 (2 cases) Brun et al., 2020 Dixon et al., 2020 Efe et al., 2020 Hanafi et al., 2020 Hayashi et al., 2020 Le Guennec et al., 2020 Moriguchi et al., 2020 Novi et al., 2020 Pilotto et al., 2020 Poyiadji et al., 2020 Wong et al., 2020 Zanin et al., 2020	Hung et al., 2003 Lau et al., 2004	Arabi et al., 2015 (3 cases) Kim et al., 2017
Myoclonus, n/N	3/98 3%	0	0
References	Rabano Suarez et al., 2020 (3 cases)		
Myelitis, n/N	6/98 6%	0	0
References	Alketbi et al., 2020 Durrani et al., 2020 Munz et al., 2020 Sarma et al., 2020 Sotoca et al., 2020 Valiudinet al. 2020		
Acute cerebrovascular disease, n/N	46/98 47%		
Acute ischemic Stroke, n/N	26/98 27%	5/11 45%	0
References	Avula et al., 2020 (4 cases) Beyrouti et al., 2020 (6 cases) Fara et al., 2020 (3 cases) Mirzaee et al., 2020 Morassi et al., 2020 (4 cases) Morassi et al., 2020 Oxley et al., 2020 (4 cases) Zhang et al., 2020 (3 cases)	Umapathi et al., 2004 (5 cases)	
Intracranial hemorrhage, n/N	7/98 7%	0	2/10 20%
References	Al-olama et al., 2020 Morassi et al., 2020 (2 cases) Garcia-Garcia et al., 2020 (4 cases)		Al–Hameed et al., 2017 Algahtani et al., 2016
Cerebral venous thrombosis, n/N	8/98 8%	0	0
References	Cavalcanti et al., 2020 (3 cases) Chougar et al., 2020 Hemasian et al., 2020 Hughes et al., 2020 Poillon et al., 2020 (2 cases)		
Posterior reversible encephalopathy syndrome, n/N	5/92 5%	0	0
References	Franceschi et al., 2020 (2 cases) Kaya et al., 2020 Kishfy et al., 2020 (2 cases)		
Patients with PNS manifestations, n/N	23/98 24% [17 references]	4/11 36% [1 reference]	5/10 50% [2 references]
Guillain–Barré syndrome, n/N	17/98 17%	0	1/10 10%

Table 2 (*Continued*)

	SARS-CoV-2 (COVID-19)	SARS-CoV (SARS)	MERS-CoV (MERS)
References	Alberti et al., 2020 Arnaud et al., 2020 Bigaut et al., 2020 (2 cases) Camdessanche et al., 2020 Coen et al., 2020 Ottaviani et al., 2020 Padroni et al., 2020 Pfefferkorm et al., 2020 Scheidl et al., 2020 Sedaghat et al., 2020 Toscano et al., 2020 (5 cases) Virani et al., 2020		Kim et al., 2017
Variants of Guillain–Barré syndrome, n/N	4/98 4%	0	0
References	Caamaño et al., 2020 Dinkin et al., 2020 Gutiérrez-Ortiz et al., 2020 (2 cases)		
Oculomotor nerve palsy, n/N	2/98 2%	0	0
	Dinkin et al., 2020 Wei et al., 2020		
Critical illness neuropathy and/or myopathy, n/N	6/98 6%	4/11 36%	4/10 40%
	Madia et al., 2020	Tsai et al., 2004 (4 cases)	Kim et al., 2017 (3 cases) Algahtani et al., 2016

the proportion of encephalopathy and encephalitis was 14% in the case reports patients (14/98, Table 2), 13% in the UK-wide surveillance study (16/152) [7], and respectively 13% (8/64), 49% (21/43) and 40% (88/222) in the cohort of Kremer et al. [9], Paterson et al. [8] and Meppiel et al. [10].

Encephalopathy and encephalitis encompass a wide range of clinical and radiological entities, as shown by the 14 patients reported in case reports or series (Table 3) and the 142 patients described in five of the cohort studies (Table 1) [4,5,8–10]. Neurological manifestations occurred from 0 to 34 days after the first signs of COVID-19 and included altered consciousness with confusion, delirium or comatose state, neuropsychiatric changes, seizure, focal neurological sign, and abnormal movements. The results of cerebrospinal fluid (CSF) examination were available for 109 out of the 156 patients and showed mild pleiocytosis (white blood cells (WBC) $\geq 5/mm^3$) in 26/156 (17%), raised protein level (≥ 0.4 g/L) in 41/156 patients (26%). Intrathecal oligoclonal bands synthesis was present in five patients out of 20 tested (25%), and SARS-CoV-2 PCR was positive in four out of 92 tested (4%). Brain imaging was performed in all patients including magnetic resonance imaging (MRI) in 127 patients (81%) and allowed to categorize patients in different categories: 1/non-specific COVID-19-related encephalopathy ($n = 86$) [4,5,8,10]: delirium and/or neuropsychiatric changes and/or seizures, without pleiocytosis or brain imaging abnormalities consistent with inflammation, but microvascular acute lesions in nine patients [4,10]; 2/acute demyelinating encephalomyelitis (ADEM, $n = 13$) [8,9,12–14] including one patient with the acute hemorrhagic leukoencephalopathy form [8] and two patients with restricted diffusion lesions raising the question of CNS small vessel vasculitis as differential diagnosis [12,13]; 3/acute necrotizing encephalopathy (ANE, $n = 4$) [9,15,16]; 4/limbic encephalitis ($n = 9$) [5,8–10,17,18]; 5/Bickerstaff's brainstem encephalitis ($n = 5$) [5,8,10,19]; 6/encephalopathy with focal or diffuse leptomeningeal abnormalities ($n = 13$) [9,10]; 7/miscellaneous encephalopathy and encephalitis with other clinical or radiological findings: encephalitis with pleiocytosis and normal brain MRI ($n = 9$) [10,20,21], encephalitis with akathisia and chorea ($n = 1$) [5], cytotoxic lesion of the corpus callosum ($n = 3$) [9,10,22], focal or multifocal cortical FLAIR hyperintensities ($n = 2$) [4,23], white matter and/or basal ganglia lesions without mention of ADEM or ANE ($n = 11$) [9,10,24]. Other central neuroinflammatory syndromes have been reported in COVID-19 patients, such as generalized myoclonus and mild hypersomnia ($n = 3$) [25], acute parkinsonian syndrome ($n = 2$) [26,27], hypothalamus and pituitary stalk involvement in patients with ophthalmoparesis ($n = 2$) [28]. More detailed imaging studies provided interesting results. Cerebral angio-MRI in five COVID-19 patients with encephalopathy showed an abnormal contrast enhancement in the basal skull wall vessel, without stenosis of the lumen, thickening of the vessel walls or parenchymal ischemic lesion, leading the authors to suggest a presumptive diagnosis of endothelitis rather than vasculitis [29]. Brain FDG-PET findings in five other patients with COVID-19 related encephalopathy had a common pattern of hypometabolism in the prefrontal or orbitofrontal cortices and hypermetabolism in the cerebellar vermis [29]. Overall, four patients had positive antibodies, antiGD1b IgG positive in three, antiCaspr2 IgG in one [5]. Electroencephalogram (EEG) was described in nine patients with CNS involvement [5,8,20,21,23,24] with seizure or status epilepticus in three, generalized slowing in three, normal in three. Two studies among COVID-19 patients have suggested a possible specific

Table 3 – Encephalopathy and encephalitis associated with SARS-CoV-2: case reports (n = 14).

Case report	Sex, M/F Age, years	Symptoms and abnormalities on clinical examination	Days[a]	Brain MRI	Electro-encephalogram	CSF	Neurological treatment and outcome	Diagnosis
Bernard–Valnet et al.	F 64	Disorientation, attention deficit, dysexecutive syndrome, psychotic symptoms (mystic delusions and visual hallucinations)	5	Normal	Status epilepticus	17 WBC/mm^3 Proteins 0.47 g/L SARS-CoV-2 PCR negative	Clonazepam and vaproate Resolution in 96 hours	Meningo-encephalitis
Bernard-Valnet et al.	F 67	Intense wake-up headache, altered mental status with dysexecutive syndrome, left hemianopia, sensory hemineglect	17	Normal	NA	21 WBC/mm^3 Proteins 0.46 g/L SARS-CoV-2 PCR negative	Resolution in 24 hours	Meningo-encephalitis
Brun et al.	F 54	Altered mental status without focal neurologic deficit	8	Multiple supratentorial punctiform and tumefactive lesions of white matter, involving corpus callosum: hypersignal on flair and DWI with restricted diffusion. 10 day after: enhancement of all lesions (No lesion in spine MRI)	NA	Normal CSF SARS-CoV-2 PCR negative	Steroid treatment Outcome: NA	ADEM? Small-vessel vasculitis?
Dixon and al.	F 59	Generalized seizure, altered consciousness without focal neurologic deficit	10	Symmetrical hemorrhagic lesions in brain stem, amygdalae, putamina, thalamic nuclei, subinsular regions, splenium of corpus callosum, cingulate gyri, subcortical perirolandic regions	NA	4 WBC/mm^3 Proteins 2.3 g/L SARS-CoV-2 PCR negative	Steroid therapy Death 8th day of admission	ANE
Efe et al.	F 35	Headache, nausea, dizziness and drug-refractory seizures	NA	Hyperintense signal in the left temporal lobe on FLAIR Suspicion of high-grade glioma: left anterior temporal lobectomy with encephalitis features on histopathological examination	NA	NA	Antiepileptic medication and temporal lobectomy Resolution of symptoms	Encephalitis with temporal involvement
Hanafi et al	M 65	Altered consciousness after discontinuation of sedation	NA	FLAIR and DWI hyperintense lesions within the periventricular white matter, basal ganglia, cerebellar peduncles and corpus callosum. Patchy enhancement of all lesions in particular globus pallidus bilaterally, with a punctuate pattern in the cerebellum. Microhemorrhage of bilateral globus pallidus.	NA	NA	NA	CNS vasculitis-like pattern (or ADEM?)
Hayashi et al.	M 75	Upper limb bilateral marked dysmetria and mild ataxic gait, then disorientation	0	Hyperintensity in the splenium of corpus callosum	NA	NA	Steroid therapy Resolution of neurologic symptoms in 48 hours, death following respiratory failure 12th day of admission	Mild encephalopathy with a reversible splenial lesion

Table 3 (*Continued*)

Case report	Sex, M/F Age, years	Symptoms and abnormalities on clinical examination	Days[a]	Brain MRI	Electro-encephalogram	CSF	Neurological treatment and outcome	Diagnosis
Le Guennec et al.	M 69	Status epilepticus	5	Hyperintensity of the right orbital prefrontal cortex and to the right caudate nucleus. No gadolinium enhancement	Repetitive 1 Hz rhythmic burst over the right frontal region	1 WBC/mm^3 Proteins 0.66 g/L SARS-CoV-2 PCR negative	Antiepileptic medication and IV Ig Clinical improvement with persistence of frontal lobe syndrome Normal MRI at day 30	Post-immune encephalitis or septic associated encephalopathy?
Moriguchi et al.	M 24	Altered consciousness and generalized seizures	9	Hyperintensity along the wall of inferior horn of right lateral ventricle on DWI. Hyperintensity of the right mesial temporal lobe and hippocampus on FLAIR. No contract enhancement	NA	14 WBC/mm^3 Proteins NA SARS-CoV-2 PCR positive	Antiepileptic medication Persistent impaired consciousness 15th day of admission	Encephalitis with mesiotemporal hyperintensity (or ictal changes?)
Novi et al.	F 64	Severe visual loss, sensory deficit on her right leg, pyramidal sign on her left leg, mild behavorial abnormalities, headache	21	Multiple T1 post-gadolinium enhancing lesions of the brain, associated with a single spine cord lesion at the T8 level and with bilateral optic nerve enhancement	NA	22 WBC/mm^3 Proteins 0.45 g/L SARS-CoV-2 PCR positive No oligoclonal bands	High dose steroids and IV Ig Significant improvement 14th day of treatment	ADEM
Pilotto et al.	M 60	Altered consciousness, irritability, confusion, akinetic syndrome associated to mutism	0	No lesion, no contrast enhancement	Generalized slowing with decreased reactivity to acoustic stimuli	18 WBC/mm^3 Proteins 0,70 g/L SARS-CoV-2 PCR negative No oligoclonal bands	High dose steroids Resolution of symptoms 11th day of admission	Encephalitis
Poyiadji et al.	F 60	Altered mental status	0	Hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, subinsular regions.	NA	Traumatic lumbar puncture SARS-CoV-2 PCR NA	IV Ig Outcome: NA	ANE
Wong et al.	M 40	Unsteady gait, diplopia, oscillopsia, limb ataxia, altered sensation in the right arm, hiccups, bilateral facial weakness. Intact peripheral reflexes	13	Increased signal lesion in the right inferior cerebellar peduncle, extending to involve a small portion of the upper cord, with edema and microhemorrhage	NA	14 WBC/mm^3 Proteins 0.42 g/L SARS-CoV-2 PCR NA	Spontaneous and partial improvement 11th day of admission, without any treatment	Rhomb-encephalitis

Table 3 (*Continued*)

Case report	Sex, M/F Age, years	Symptoms and abnormalities on clinical examination	Days[a]	Brain MRI	Electro-encephalogram	CSF	Neurological treatment and outcome	Diagnosis
Zanin et al.	F 54	Altered consciousness associated without focal sign	0	T2WI hyperintense lesion of white matter, without restriction of diffusion nor contrast enhancement, in periventricular areas, bulbomedullary junction and cervical and dorsal cord	Fronto-temporal seizures	Normal CSF SARS-CoV-2 PCR negative	High dose steroids Partial improvement 12th day of admission	Encephalopathy with demyelinating lesions

[a] Neurological signs after the first signs of COVID-19.

electroencephalographic pattern showing monomorphic biphasic delta slow waves with a periodic organization in the frontal areas [30,31].

Neurological short-term prognosis was available for 26 patients in the case reports (Table 3) or case series [29,32,33] and 116 patients in cohort studies [4,5,8–10]. A complete or partial recovery was noted in 109/142 patients (77%) either spontaneously (n = 68) or with immunotherapy (n = 41) including high-dose steroid treatment and/or intravenous immunoglobulins (IV Ig). Among the 109 patients, 17 died (12%). In the study of Meppiel et al., COVID-19 patients with encephalopathy had a high mortality rate (10/67, 15%) compared to patients with encephalitis (1/21, 5%).

Neuropathological studies have provided evidence for different patterns of CNS damage. To date, only one autopsy study with six patients [34] has demonstrated the presence of lymphocytic panencephalitis and meningitis, associated in younger patients with diffuse petechial brain hemorrhages. Other studies have reported several hypoxic and hemorrhagic neuropathological changes in severe COVID-19 patients, such as acute hypoxic injury in the cerebrum and cerebellum [35], widespread hemorrhagic white matter lesions and neocortical infarcts [36–38], with no thrombi, encephalitis or vasculitis. One study found microglia activation in the brainstem of seven COVID-19 patients with strong systemic inflammation, but not more pronounced than in septic controls [39]. These studies did not support evidence for virus infiltration, and only a single autopsy case so far documented the presence of SARS-CoV-2 in endothelial and neural cells of frontal lobe sections [40].

The heterogeneity of clinical, radiological and pathological pictures suggests that different pathogenic pathways are involved. A first hypothesis is that SARS-CoV-2 could invade the CNS and induce brain lesions either by direct infiltration or by immune-mediated response. To date, there is no strong argument for direct neuropathogenicity, as the presence of SARS-CoV-2 is only exceptionally demonstrated in patients' CSF and in the brain after autopsy studies, and as neurological prognosis of patients with encephalitis or encephalopathy was most often favorable. An immune-mediated mechanism is probable, given the typical post-infectious syndrome reported such as ADEM, ANE, Bickerstaff's encephalitis or generalized myoclonus. Another hypothesis is that CNS damage reflects a more generalized systemic response. Indeed, the release of pro-inflammatory cytokines is thought to play a central role in severe COVID-19 [41] and is one of the key pathogenic pathways described in septic-associated encephalopathy (SAE) [42]. SAE characteristics are similar in some regards to the encephalopathy described in COVID-19 patients: age, illness severity, acute vascular lesion with some posterior reversible encephalopathy syndromes (PRES) [43], of which several cases have been reported in COVID-19 patients [3,44]. The cytokine storm is also suspected of being involved in cytotoxic lesions of the corpus callosum, described in COVID-19 adult patients [9,22] and pediatric patients [45–47]. Some histopathological findings also supported the hypothesis of a critical illness-related encephalopathy [39]. Finally, endothelitis [29,48] and microvascular injury [37,38] may play a role in the pathogenesis of the encephalopathy,

3.2. Myelitis

Acute myelitis in COVID-19 patients is rare, as only six patients have been described in case series (Table 2) [49–54] and one patient was reported in a cohort study but not described (Table 1) [8]. Among the six patients, involving three men and three women aged 24 to 69, spine MRI showed extensive myelitis in almost all patients (5/6, 83%), throughout the spinal cord in two patients [49,52], over seven to 12 vertebrae in three other patients [50,53,54], with one exhibiting central necrosis at one level [53]. Neurological symptoms started two to 10 days after the onset of COVID-19. Lymphocytic pleiocytosis was present in four out of five CSF examinations. All patients were considered as post-infectious myelitis, treated with immunotherapy (methylprednisolone in all, plasma exchange in three) with significant clinical improvement.

3.3. Stroke

A reduction in global stroke admission was observed during the COVID-19 outbreak but is not yet fully understood [55]. Acute cerebrovascular diseases were reported in a proportion of 0.7 to 5.8% among hospitalized COVID-19 patients [2–6] with predominant acute ischemic stroke (AIS) followed by intracranial hemorrhage (ICH), cerebral venous thrombosis (CVT) and PRES (Table 1).

Among neurological manifestations, acute cerebrovascular disease represents half of the case reports (Table 2) and half of patients included in the UK-wide surveillance study [7], but only 1 to 25% in the other cohort studies [2–6,10]. The causal relationship between SARS-CoV-2 and stroke have not yet been demonstrated but a recent study showed that the risk of stroke was significantly higher with SARS-CoV-2 infection than with influenza infection, after adjustment for vascular risk factors [56].

3.3.1. Acute ischemic strokes

AIS occurred in 1.3 to 4.7% of COVID-19 patients [3–6], independently of COVID-19 severity [3]. No previous respiratory or general symptoms were reported before stroke in 26 to 48% of COVID-19 patients [10,56,57] and the mean time of occurrence was five to 12 days after the first COVID-19 symptoms [3,10,57]. Six small cases series [58–63] and two case reports [64,65] detailing a total of 26 patients (Table 2) highlighted the occurrence of large vessels stroke [59,60,62], and the high elevation of D-dimer level [59,62]. Vascular risk factors were present in 20/26 patients (77%) and only a few cases (4/26, 15%) [60,62] concerned young patients under 40 without any medical history. Median age in cohort studies ranged from 65 to 71 years [10,56,57,66].

A study [67] that compared the clinical characteristics of AIS patients with COVID-19 to AIS patients without COVID-19 demonstrated that COVID-19 patients were younger, had higher admission National Institutes of Health Stroke Scale Score (NIHSS), higher peak D-dimer level, were more likely to have cryptogenic stroke subtype and a proximal large vessel occlusion, were more likely to be treated with anticoagulation, and had a higher inpatient mortality. The global COVID-19 Stroke registry including 174 patients from 16 countries confirmed that AIS patients with COVID-19 had a higher risk for severe disability and death [66].

Cryptogenic stroke has been reported in 53 to 67% of AIS in COVID-19 patients [10,57]. Considering that brain ischemic events could be at least in part attributable to SARS-CoV-2 infection, different mechanisms may be discussed. First, a procoagulant state has been demonstrated in particular in the most severe patients [68], in line with the high D-Dimer level noted in several AIS patients with COVID-19. Second, in an autopsy series of COVID-19 patients, an aspect of endothelitis with viral inclusions and diffuse inflammation of the vascular endothelium was identified [48] but, to date and to our knowledge, there is no confirmed case of CNS vasculitis in COVID-19 patients. The few neuropathological data showed signs of thrombotic microangiopathy and endothelial injury, with no evidence of vasculitis or necrotizing encephalitis [57]. A third possible mechanism is cardio-embolic stroke, as cardiac arrythmia and acute myocarditis are part of cardiovascular manifestations reported in COVID-19 patients [69]. Cardioembolism was determined as the cause of AIS in respectively 15% and 24% of COVID-19 patients in two studies [10,57]. Finally, other rare causes of AIS have been reported in COVID-19 patients, including five cases of cervical artery dissections [3,57,64] and one case of focal cerebral arteriopathy in a 12-year-old boy [65].

3.3.2. Other acute cerebrovascular diseases

ICH, CVT and PRES have been the subject of several case reports (Table 2) but their prevalence is very low, under 1% for each [3–6,57] (Table 1).

ICH was only noticed in patients suffering severe disease. Considering the seven published cases of ICH in COVID-19 patients (Table 2), the five cases reported in the study of Hernández–Fernández et al. [57] and the five cases reported in the study of Meppiel et al., the characteristics of ICH were the following: unique or multiple lobar ICH ($n = 10$) [10,57,61,70,71], deep ICH ($n = 3$) [10,57], small pontin hemorrhage ($n = 2$) [70] and cerebellar ICH ($n = 2$) [10,61], with a fatal outcome in 8/17 patients (47%). Otherwise, among the five cases of PRES in COVID-19 patients [44,72,73] (Table 2), four exhibited petechial hemorrhage (80%) and all had a good outcome. One could hypothesize that PRES and multiple ICH could be linked to systemic damage induced by severe COVID-19, but precise pathogenic mechanisms remain to be clarified.

Finally, eight COVID-19 patients with CVT have been reported (Table 2), probably linked to COVID-19 coagulopathy [68] and highlighting an unusual majority of men ($n = 5$, 63%) and an unusual high rate of fatal cases ($n = 4$, 50%).

3.4. Seizures

Seizure is an uncommon neurological symptom reported in less than 1% of hospitalized COVID-19 patients [2–4] (Table 2) and probably not related to SARS-CoV-2 infection [74]. However, a recent study showed that de novo seizures were detected in twp out of 22 continuous electroencephalographies performed in COVID-19 patients [75]. Further studies are

necessary to clarifying the risk of seizure in SARS-CoV-2 infection.

3.5. *Guillain–Barré Syndrome (GBS) and variants*

GBS was reported in less than 0.5% of hospitalized COVID-19 patients [3–6] (Table 1). Among neurological manifestations, GBS and variants represent 21% of the case reports (Table 2), 8% of patients included in the UK-wide surveillance study [7], 0 to 7% in the other cohort studies [2–6,10]. Interestingly, an Italian study has demonstrated that the incidence of GBS increased in their region during the COVID-19 epidemic compared with the three previous years [76].

Seventeen COVID-19 patients with GBS have been reported in case reports and case series (Table 2) [77–88] and 14 patients in the study of Meppiel et al. [10]. The characteristics of these 31 patients were the following: 24 were male (77%), age ranged from 20 to 84. Neurological symptoms occurred four to 35 days after the onset of COVID-19. The electromyogram was suggestive of demyelination in 25 out of 29 examinations (86%) and of an axonal variant in four patients (14%). CSF was analyzed in 28 patients and showed albuminocytologic dissociation in 19 cases (68%), mild pleiocytosis in two case (7%), negative SARS-CoV-2 PCR in the 21 tested cases. Antiganglioside antibodies testing was negative in the nine performed. All patients were treated with IV Ig, nine of them (29%) required mechanical ventilation.

Some variants of GBS were described in COVID-19 patients (Tables 1 and 2). Considering the case reports, series and cohort studies, we identified three cases of Miller Fisher syndrome [4,89,90], two cases of facial diplegia [10,91] and two cases of polyneuritis cranialis [5,90]. Six cases of isolated oculomotor neuropathy have also been described with no evidence for GBS or variants [5,8,10,89,92].

3.6. *Muscular injury*

A recent study reported six patients developing acute flaccid quadriplegia after intensive care management, whose clinical and electrophysiological characteristics suggested critical illness myopathy [93]. To date, while myalgia is a common symptom in COVID-19 patients (Table 2), no other myopathies such as viral or inflammatory type have been described.

3.7. *Anosmia and ageusia*

Anosmia is noted in about 5% of hospitalized COVID-19 patients in cohort studies (Table 1) [2,3,6] whereas its prevalence reached 34 to 86% in dedicated surveys [94,95]. Furthermore, a study [96] in patients with influenza-like illness showed a strong association between hypogeusia/hyposmia and a diagnosis of COVID-19.

Smell and taste disorders appear early in the course of the COVID-19 disease [3,94] and tend to persist after the improvement of other symptoms, with regression within the first eight days following the resolution of the disease for 70% of patients [95]. The pathogenesis of olfactory and taste disorders remains unclear, moreover this rapid recovery seems hardly compatible with a direct viral induced damage of sensory neurons and/or olfactory bulb.

4. Neurological manifestations associated with other human coronaviruses (HCoV)

We have identified 10 articles reporting 22 cases of neurological manifestations associated with other HCoV, including 11 in SARS-CoV infection, 11 in MERS-CoV infection and only one in HCoV-43 infection (Table 2). Seven patients reportedly had encephalopathy or encephalitis: two SARS patients [97], with altered mental status and positive SARS-CoV PCR in the CSF [98]; three MERS patients with encephalopathy and plurifocal involvement of the white matter suggestive of ADEM [99], a MERS patient with Bickerstaff's encephalitis [100]; one young patient with ADEM and detection of HCoV-OC43 in the CSF [101]. Seven other published cases reported neurovascular disorders, with large artery ischemic stroke in five SARS patients [102] and fatal lobar intracranial hemorrhage in two MERS patients [103,104]. Among peripheral manifestations, only one case of GBS was reported in a MERS-patient [100], other acute neuropathies associated with SARS ($n = 4$) [105] or MERS ($n = 4$) [100,103] were considered as critical illness polyneuropathy and/or myopathy.

An autopsy study involving eight patients highlighted the presence of SARS-CoV in the brain, located within cytoplasm neurons in the cortex and the hypothalamus [106]. There are no published postmortem data from MERS patients. Otherwise, several studies have demonstrated the presence of the HCoV-OC43 in brain samples from autopsies of patients with multiple sclerosis [107].

Altogether, these clinical and neuropathological data are consistent with neuroinvasion, especially for SARS-CoV. However, the presence of this pathogen in the brain does not prove its neuropathogenicity, be it direct or immune-mediated. The existence of neurovascular manifestations associated with MERS and SARS, however scarce they may be, also reinforces the hypothesis of a mechanism of coagulopathy and/or endothelial damage in emerging human coronaviruses.

5. Conclusion

Previous clinical data about human coronaviruses were consistent with neuroinvasion, especially for SARS-CoV whose presence has been detected in brain autopsies and in the CSF of patients presenting CNS manifestations. The heterogeneity of clinical, radiological and pathological descriptions of neurological manifestations associated with COVID-19 suggests that different pathogenic pathways are involved. To date, there is no strong argument for direct neuropathogenicity as the presence of SARS-CoV-2 is only exceptionally demonstrated in patients' CSF or in the brain after autopsy studies, and as neurological prognosis of patients with encephalitis or encephalopathy was most often favorable. Indeed, most cases of encephalopathies are reminiscent of septic-associated encephalopathy and share the same context of systemic inflammatory response and sometimes ''cytokine storm''. Post-infectious immune-mediated mechanisms such as ADEM, generalized myoclonus, acute transverse myelitis, Guillain–Barré syndromes and variants

have been reported. Finally, strokes in COVID-19 patients were significantly more severe and associated with a poorer outcome when compared to other stroke patients and this could be related to COVID-19 coagulopathy and/or endothelitis which have been widely described. Recognition and understanding of these different entities and of their underlying pathological mechanisms is important to improve the clinical management of COVID-19 patients with neurological manifestations.

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