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Short communication

Infectious and immune-mediated central nervous system disease in 48 COVID-19 patients

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ABSTRACT

Objectives: To summarise and discuss current knowledge about SARS-CoV-2-associated infectious/immune-mediated central nervous system (CNS)-disease.

Method: Literature review.

Results: Altogether 28 articles were found, which reported 48 patients with SARS-CoV-2-associated infectious/immune-mediated CNS-disease. Age ranged from 22 to 79y. There was male preponderance. There were 14 patients with infectious CNS-disease (meningitis (n = 1), encephalitis (n = 5), meningo-encephalitis (n = 5), myelitis (n = 3)), and 34 patients with parainfectious CNS-disease (encephalopathy (n = 18), autoimmune encephalitis (n = 11), acute, disseminated, encephalo-myelitis (n = 3), acute, haemorrhagic, necrotizing encephalopathy (n = 2)). The cerebrospinal fluid (CSF) was tested for SARS-CoV-2 in 40 patients and was positive for the virus in 4 patients with infectious CNS-disease but was negative for the virus in all patients with parainfectious CNS-disease. Immune-modulating treatment may be more effective than virostatics/antibiotics for SARS-CoV-2-associated infectious/parainfectious, non-vascular, non-hypoxic CNS-disease. In patients with autoimmune encephalitis plasmapheresis may be beneficial. Twenty-two patients recovered, 2 did not, and 6 patients died.

Conclusions: SARS-CoV-2 can cause infectious/immune-mediated CNS-disease. The CSF is positive for virus-RNA in only few patients with infectious CNS-disease but negative for virus-RNA in immune-mediated CNS-disease, suggesting an immune-mediated pathophysiological mechanism. The outcome of SARS-CoV-2-associated infectious/immune-mediated CNS-disease is favourable in the majority of cases but can be fatal in single cases.

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1. Introduction Brief communication

It is now well appreciated that SARS-CoV-2 not only affects the respiratory system but almost all organs to variable degrees. SARS-CoV-2 can be even found in the central and peripheral nervous system (CNS, PNS) [1]. CNS manifestations of SARS-CoV2 include meningitis/encephalitis, ventriculitis/endothelialitis, myelitis, encephalopathy, auto-immune encephalitis (AIE), acute, hemorrhagic, necrotising encephalopathy (AHNE), acute disseminated encephalomyelitis (ADEM), ischemic/hemorrhagic stroke, sinus venous thrombosis (SVT), intra-cerebral bleeding, and cerebral hypoxia [2]. This literature review aims at summarising and discussing recent advances concerning infectious and immune-mediated CNS-disease in SARS-CoV-2-infected (COVID-19)

patients. Cerebro-vascular disorders, such as ischemic stroke, cerebral bleeding, or sinus venous thrombosis and cerebral hypoxia secondary due to pulmonary disease were not considered.

Altogether, 28 articles reporting 48 patients with infectious or immune-mediated SARS-CoV-2-associated CNS-disease were included [3–30]. Patients originated from Turkey (n = 11), France (n = 9), USA (n = 9), China (n = 4), UK (n = 4), Italy (n = 2), Switzerland (n = 2), Spain (n = 2), Japan, (n = 1), India (n = 1), Germany (n = 1), Ecuador (n = 1), and Dubai (n = 1). Age ranged from 22 to 79y (table 1). There was male preponderance. In 43 patients CNS-disease started after onset of COVID-19 and in 4 patients before onset of COVID-19 (table 1). Clinical manifestations included seizures (n = 11), confusion (n = 7), impaired consciousness (n = 6), headache (n = 5), psychosis/delirium (n = 5), muscle weakness (n = 4), and dysphagia (n = 2). Among patients with infectious CNS-disease (n = 14), 1 presented with meningitis, 5 with encephalitis, 5 with meningo-encephalitis, and 3 with myelitis [10,11] (table 1). In one patient meningo-encephalitis was the

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Table 1
Patients with SARS-CoV-2-associated infectious and immune-mediated CNS disease so far reported.

Age(y)	Sex	Onset	OO(d)	M/E	LP	CIC	CM	Imaging	Treatment	OC	Country	Reference
Infectious												
24	m	B	5	E	nr	yes	HA, IC, SE	Edema, ventriculitis	VS, AB, MV, S, AED	nr	Japan	[3]
44	f	A	3	E	yes	nr	CON, SE	E, bleeding	VS, AB, AED, S	death	India	[4]
nr	nr	nr	nr	E	nr	yes	SE, hiccups	normal	VS, AB, AED,	nr	China	[5]#
41	f	AB	0	ME	yes	no	SE, CON, HL	normal	VS, AB, CHLO, AED, S	REC	USA	[6]
36	m	A	4	ME	nr	yes	HA	SAB, ICB, SDH	Surgery	nr	Dubai	[7]
64	f	A	6	ME	yes	no	SE, psychosis	normal	VS	REC	Swiss	[8]
67	f	A	17	ME	yes	no	HA, CON, HAN, HN	normal	VS, AB	REC	Swiss	[8]
69	m	A	7	ME	yes	no	HA, CON, fall	normal	VS, AB, CHLO	REC	France	[9]
66	m	A	>5	Myelitis	nr	nr	paraparesis	nr	VS, AB, S, IVIG	REC	China	[10]
60	m	A	8	Myelitis	yes	no	paraparesis	myelitis	VS, AB, S	REC	German	[11]
Immune-mediated												
49	m	A	nr	AIE	no	no	nr	E	AB, PE	REC	Turkey	[12]
59	m	A	nr	AIE	no	no	nr	E	AB, PE	REC	Turkey	[12]
59	m	A	nr	AIE	no	no	nr	normal	AB, PE	death	Turkey	[12]
51	f	A	nr	AIE	no	no	nr	normal	AB, PE	REC	Turkey	[12]
55	m	A	nr	AIE	no	no	nr	normal	AB, PE	ICU	Turkey	[12]
22	m	A	nr	AIE	no	no	nr	E	AB, PE	REC	Turkey	[12]
71	m	A	nr	ADEM*	nr	nr	nr	nr§	ICU, S	death	USA	[13]
40	f	A	11	ADEM	no	no	bulbar signs	demyel	AB, IVIG, CHLO	REC	USA	[14]
54	f	A	days	ADEM	no	no	SE	demyel	AED, S	REC	Italy	[15]
~55	f	A	3	AHNE	nr	no	CON	AHNE	IVIG	nr	USA	[16]
59	f	A	10	AHNE	no	no	SE, IC	edema	MV, S	death	UK	[17]
74	m	A	1	EP	no	no	HA, CON	old stroke	VS AB, CHLO, AED	ICU	USA	[18]
8 pat.	nr	A	nr	EP	nr	no	nr	LEE	nr	nr	France	[19]
60	m	B	2	EP	yes	no	IC, akinetic	normal	VS, AB, S	REC	Italy	[20]
23	m	AB	0	EP	no	nr	psychosis	normal	AB, S, IVIG, neuroleptics	REC	Ecuador	[21]
31	f	A	18	EP	yes	nr	coma	edema	VS, AB, CHLO, MV	death	USA	[22]
34	m	A	9	EP	no	nr	coma, SE	edema	CHLO, MV	nr	USA	[22]
64	m	A	nr	EP, CH	no	nr	SE	T2HI	CHLO, MV	REC	USA	[22]
46	m	B	2	EP	no	no	delirium, SE	inflammation	VS, AB, AED, MV	REC	UK	[23]
79	f	B	2	EP	no	no	SE, delirium	limbic E	AED	REC	UK	[23]
77	m	A	6	EP	nr	nr	delirium	normal	VS, AB	death	UK	[24]
69	f	A	8	myelitis	yes	no	weakness	myelitis	S, PE	REC	Spain	[25]
nr	m	A	14	E	no	no	E	normal	supportive	REC	China	[26]
56	f	A	15	M	no	no	TEPA, dysph	LEE	IVIG	REC	Spain	[27]
64	m	A	2	EP	no	no	IC, CON	normal	VS, supportive	REC	China	[28]
5 pat.	nr	A	nr	AIE	no	no	nr	CSA	MV	nr	Turkey	[29]
40	f	A	nr	E	nr	yes	syncope	nr	CHLO	REC	USA	[30]

A: onset of ME after onset of non-neurological manifestations, AB: antibiotics, AED: antiepileptic drugs, AHNE: acute, hemorrhagic, necrotizing encephalopathy, AIE: auto-immune-encephalitis, B. onset of ME before onset of non-neurological manifestations, CC: CSF-culture, CH: cerebral hypoxia, CHLO: chloroquine, CIC: SARS-CoV-2 in CSF, CM: clinical manifestations, CON: confusion, CSA: cortical signal abnormality, Demyel: demyelination, dysph: dysphagia, E: encephalitis, EP: encephalopathy, f: female, HA: headache, HAN: hemianopia, HL: hallucinations, HN: hemineglect, IC: impaired consciousness, ICB: intracerebral bleeding, ICU: intensive care unit, IVIG: intravenous immunoglobulins, LEE: leptomeningeal enhancement, LP: lymphocytic pleocytosis, M: meningitis, m: male, MB: microbleeds, MV: mechanical ventilation, nd: not done, nr: not reported, OO: latency between onset of meningitis/encephalitis and COVID-19 respectively vice versa, PE: plasma exchange, REC: recovery, S: steroids, SAB: subarachnoid bleeding, SDH: subdural hematoma, SE: seizures, T2HI: hyperintensity on T2-images, TEPA: quadraparesis, VS: virostatics, *: on autopsy, §: ADEM-like lesions, #: reported in Ramoli et al.

only manifestation of SARS-CoV-2 [6]. In one patient SARS-CoV-2-associated meningo-encephalitis was accompanied by intracerebral bleeding, subarachnoid bleeding, and subdural hematoma [7]. One patient with encephalitis additionally had ventriculitis [3]. Immune-mediated CNS-disease was far more frequent than infectious CNS-disease (table 1). Among patients with immune-mediated CNS-disease (n = 34), 18 had encephalopathy, 11 AIE, 3 ADEM, and 2 AHNE. Among the 40 patients undergoing a spinal tap, mild lymphocytic pleocytosis was found in 7 with infections and 2 with immune-mediated CNS-disease. The cerebrospinal fluid (CSF) was tested for SARS-CoV-2 in 40 patients and was positive for virus-RNA in only 4 patients with infectious CNS-disease but negative in all patients with immune-mediated CNS-disease. Fifteen patients received virostatics, 21 antibiotics, 11 steroids, 5 immunoglobulins, 7 plasma exchange, 8 anti-seizure drugs (ASDs), 8 chloroquine, and 11 required mechanical ventilation (table 1). In patients with AIE, particularly plasma exchange had a beneficial effect. Altogether, twenty-two of the 48 patients recovered, 2 did not, and 6 died. No information about the outcome was provided for the remaining patients.

This review shows that CNS disease in COVID-19 only rarely results from infection with SARS-CoV-2 but, more commonly, from the immune response to the virus. This is why immunosuppressive and immune-modulating treatment (steroids, immunoglobulins, plasma exchange), have a strong role in the management of immune-mediated CNS-disease in COVID-19 patients. The virus was found in the CSF in only four patients with infectious CNS-disease. The reason for the rare occurrence of the virus in the CSF remains speculative but possibly the virus is only transiently present in the CSF or invades neurons or glial cells immediately on arrival in the CNS. An argument in favour of the immediate invasion of neurons is that the virus has been found in neurons and endothelial cells of the frontal lobe [31]. There are even speculations that the CNS serves as a reservoir for the virus in the absence of clinical manifestations [32]. These considerations imply that virus-negative infectious CNS-disease is in fact immune-mediated. Pleocytosis does not exclude an autoimmune pathogenesis.

Arguments in favour of an immune-mediated pathogenesis of virus-negative/positive CNS-disease in COVID-19 are that several patients responded favourably to steroids, immunoglobulins, or

plasma exchange [20] and that CNS inflammatory proteins are increased in COVID-19 encephalopathy [20]. This corresponds with the general hyperinflammatory state (cytokine storm, dysregulated immune response) with massive release of cytokines and chemokines that impair blood–brain barrier permeability [20] and activate neuro-inflammatory cascades [33]. Cytokines elevated in the CSF of a 78yo female with acute encephalopathy included IL-17A, IL6, IL-8; OP-10, and MCP-1 [34]. In two cases with SARS-CoV-2 associated encephalitis cytokines elevated in the CSF were IL-1 β , IL-6, IFN-1 α , and IFB-1 β [35]. Chemokines have not been determined in the CSF is far. Chemokines elevated in the serum include CCL2/MCP-1, CCL3/MIP-1a, CXCL10/IP-10, CCL5/RANTES, and CCL20/MIP-3a [36]. Furthermore, SARS-CoV-2 infection is more severe if the number of CD8 T-killer cells is low. Elevation of neutrophils reduces CD8 T-killer cells [37]. The immunologic pathogenesis is further supported by several reports presenting only non-specific CNS abnormalities in COVID-19 patients, such as impaired consciousness, confusion, disorientation, dizziness, delirium, hallucinations, psychosis, headache, ataxia, or seizures [38].

The route via which SARS-CoV-2 enters the CNS in some cases is unknown. Generally, the virus could enter the brain via retrograde, axonal migration in certain cranial nerves, via hematogenic spread, or encapsulated in immune cells via the blood brain barrier [39]. Recently, it has been proposed that the furin-like cleavage site of the virus could be an important determinant for its neurotropism [39]. S-protein cleavage by furin or furin-like proteases not only plays a key role in the invasion and virulence of SARS-CoV and Middle East Respiratory Syndrome (MERS) but also determines the host specificity and tissue tropism of these coronaviruses [39]. However, it is currently unknown if the furin-like cleavage site on the spike-protein of SARS-CoV-2 has a specific role in its invasion of the CNS [39]. Overall, the majority of scientists believes, that there is currently no pathological evidence to support a viral infection in nerve tissue and that there is need to study brain functions in SARS-CoV-2 infected patients with neurological involvement [39].

In conclusion, SARS-CoV-2 rarely causes infectious or immune-mediated CNS-disease, such as meningitis/encephalitis, ventriculitis/endothelialitis, myelitis, encephalopathy, AIE, AHNE, or ADEM. Virus-RNA is absent in SARS-CoV-2-associated immune-mediated CNS-disease and present only in single cases with infectious CNS-disease. Treatment of infectious/immune-mediated CNS disease in COVID-19 relies on virostatics, antibiotics, antiepileptics, steroids, immunoglobulins, plasma exchange, and mechanical ventilation. The outcome of infectious and immune-mediated CNS-disease in COVID-19 patients is usually fair but can be fatal in some cases.

2. Patient consent

Not applicable.

3. Availability of data

All data are available

4. Code availability

Not applicable.

Ethical approval

The research has been given ethical approval.

CRedit authorship contribution statement

Josef Finsterer: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Fulvio A. Scorza:** Formal analysis, Investigation, Methodology, Validation, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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