

05-03-2021

COMPLICANZE NEUROLOGICHE NEI PAZIENTI COVID-19

D.ssa Federica Angelone
UOSD Malattie Infettive
Responsabile M A Di Rosolini

Introduzione

Le manifestazioni neurologiche nei pazienti con infezione da COVID-19 rientrano in tre categorie:

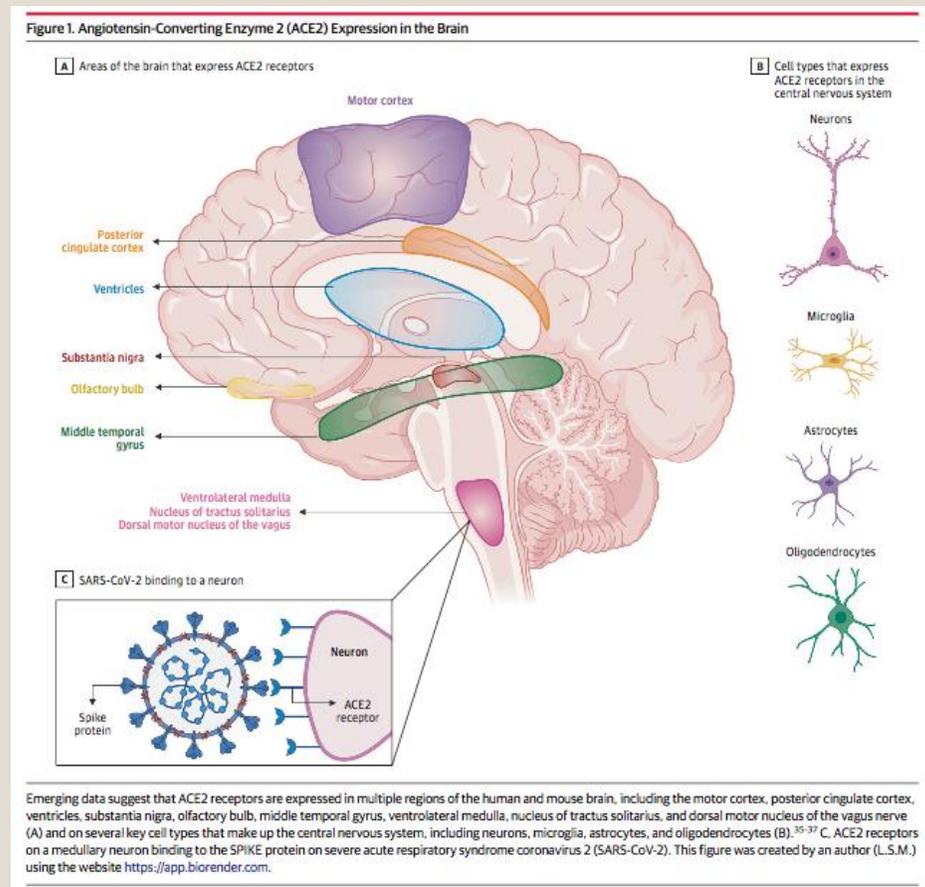
- a) espressioni neurologiche dei sintomi della malattia di base (cefalea, vertigini, disturbi dello stato di coscienza, atassia, manifestazioni epilettiche e stroke)
- b) sintomi di origine neuro-periferica (ipo-ageusia, iposmia, nevralgia);
- c) sintomi da danno muscolare scheletrico, spesso associate a danno epatico e renale

Table 2

Neurological complications and manifestations of COVID-19.

Site	Manifestations and Complications
Central Nervous System	Dizziness Headache Acute cerebrovascular disease Impaired consciousness Transverse myelitis Acute hemorrhagic necrotizing encephalopathy Encephalopathy Encephalitis Epilepsy Ataxia
Peripheral Nervous System	Hypogeusia Hyposmia, Neuralgia Guillian Barre syndrome Skeletal muscle injury

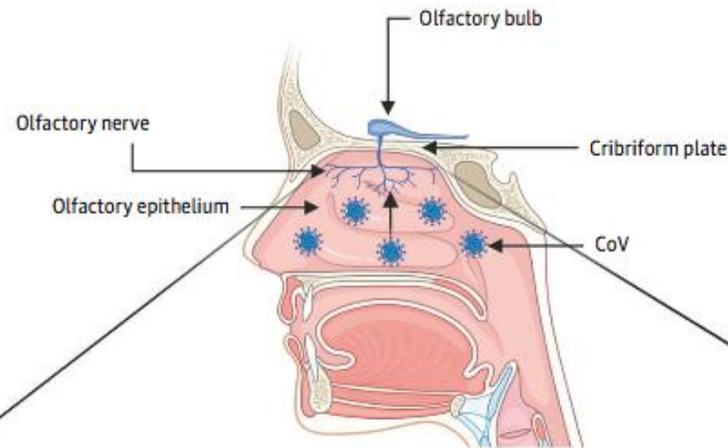
Recettori ACE-2 e Covid-19



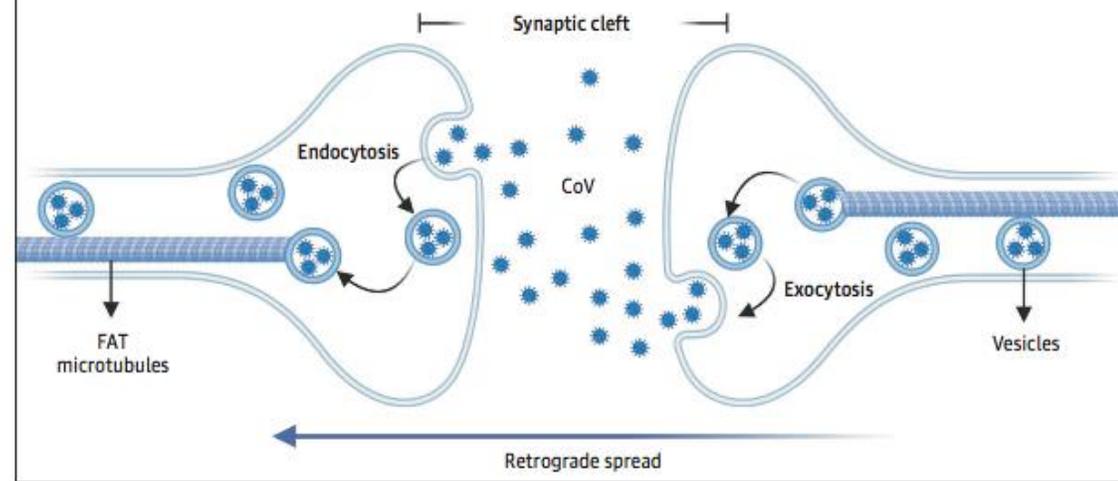
I recettori ACE2 sono espressi a livello dei neuroni, degli astrociti ed oligodendrociti. In particolare a livello della substantia nigra, i ventricoli, circonvoluzione temporale media, corteccia cingolata posteriore e bulbo olfattorio

Figure 2. Transsynaptic Viral Spread

A Spread via the transcribrial route

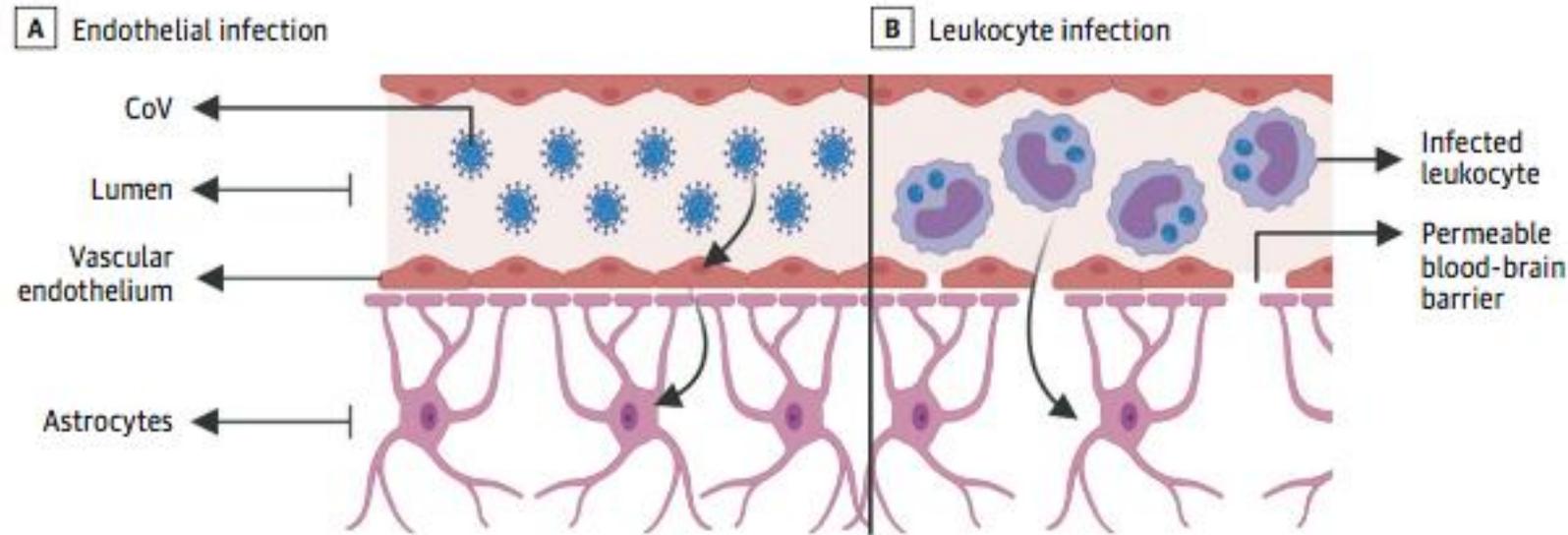


B Spread via transsynaptic transfer



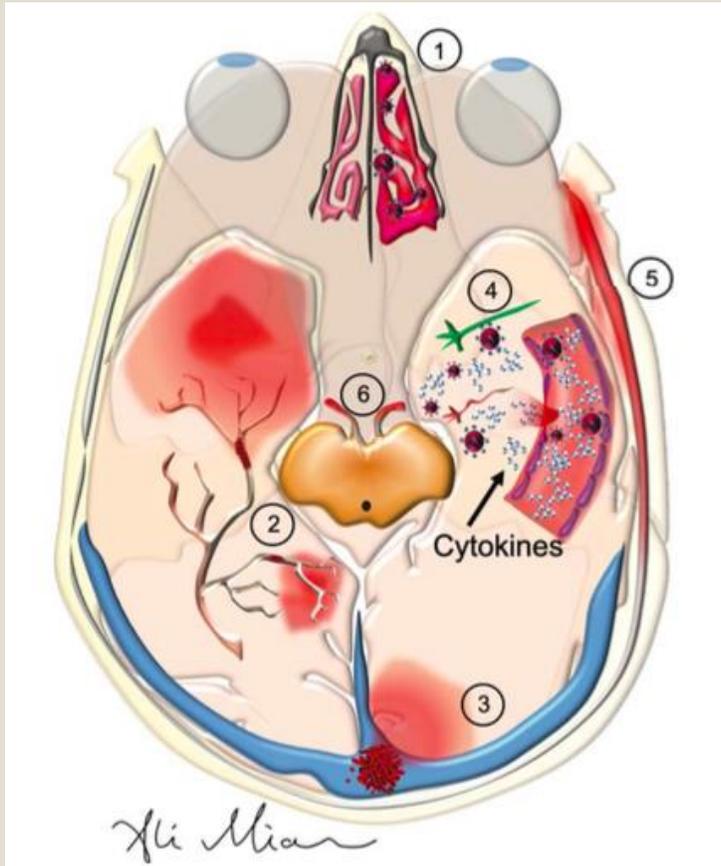
A. Coronavirus (CoV) has been shown to spread via the transcribrial route from the olfactory epithelium along the olfactory nerve to the olfactory bulb within the central nervous system. B. CoV has been shown to spread retrograde via transsynaptic transfer using an endocytosis or exocytosis mechanism and a fast axonal transport (FAT) mechanism of vesicle transport to move virus along microtubules back to neuronal cell bodies. This figure was created by an author (L.S.M.) using the website <https://app.biorender.com>.

Figure 3. Mechanisms of Spread Across the Blood-Brain Barrier



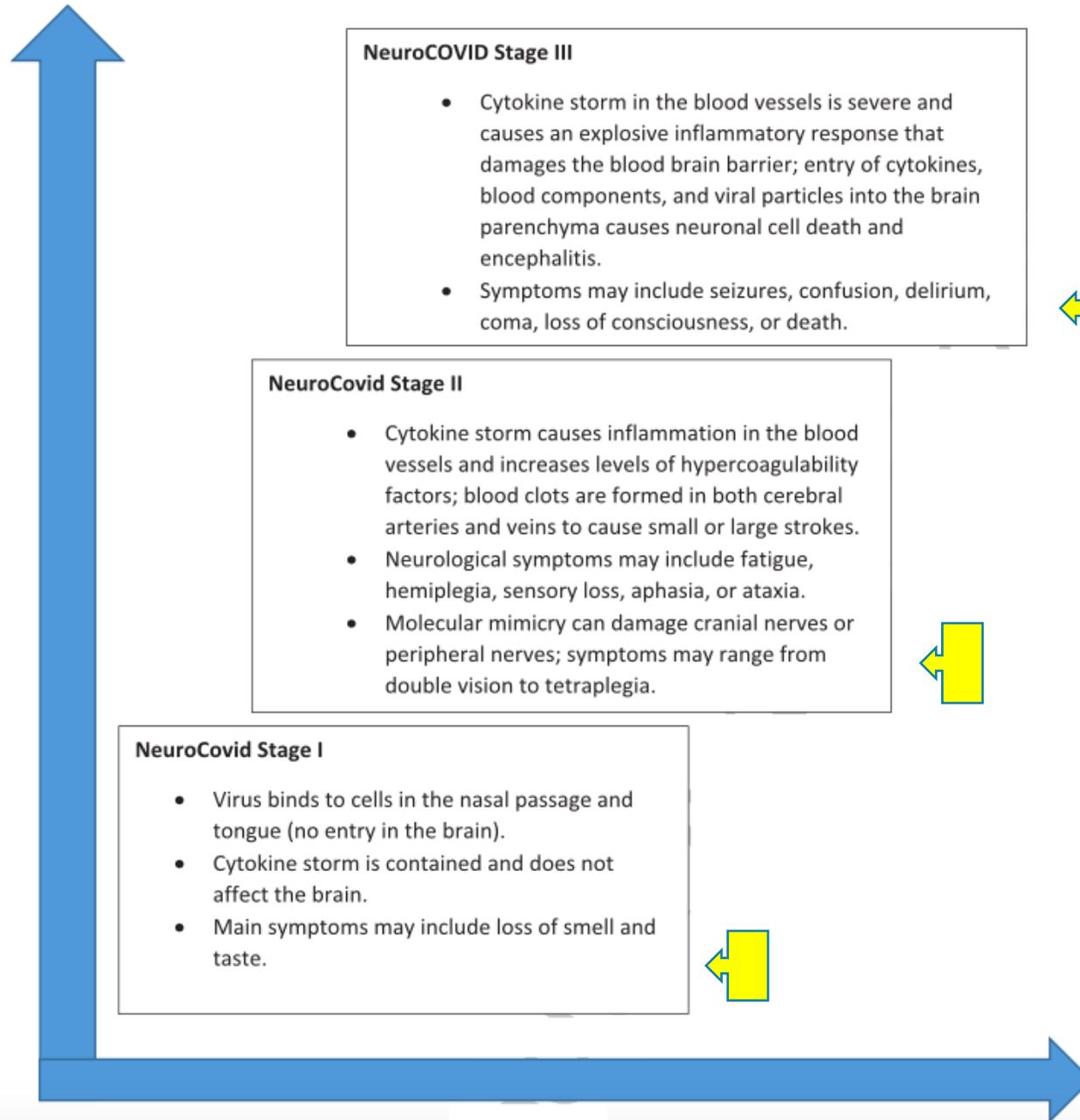
A, Infected vascular endothelial cells have been shown to spread severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to glial cells in the central nervous system. B, Known as the *Trojan horse mechanism*, infected leukocytes can cross the blood-brain barrier to infect the central nervous system. CoV indicates coronavirus. This figure was created by an author (L.S.M.) using the website <https://app.biorender.com>.

Fisiopatologia



SARS-Cov2: Pathophysiology of action in the nose, cranial nerves and the brain. SARS-Cov2 can cause a variety of neurological symptoms in patients with COVID-19 such as anosmia, strokes, encephalopathy, meningitis, and cranial nerve injury.

- 1) Legame e inibizione cellule epiteliali nasali e gustative, **riduzione del senso del gusto e dell'olfatto.**
- 2) Rilascio di citochine e pathway della coagulazione nel sangue nei piccoli e grandi vasi **occlusione a livello delle arterie cerebrali.**
- 3) Formazione di coaguli di sangue a livello delle vene cerebrali **trombosi vene.**
- 4) Alti livelli di citochine nei vasi cerebrali danneggiano la barriera emato-encefalica, **danno neuronale, cellule della glia con possibile encefalopatia.**
- 5) Danno a livello delle arterie meningee **meningite.**
- 6) Formazione di auto-anticorpi **danno nervi cranici.**



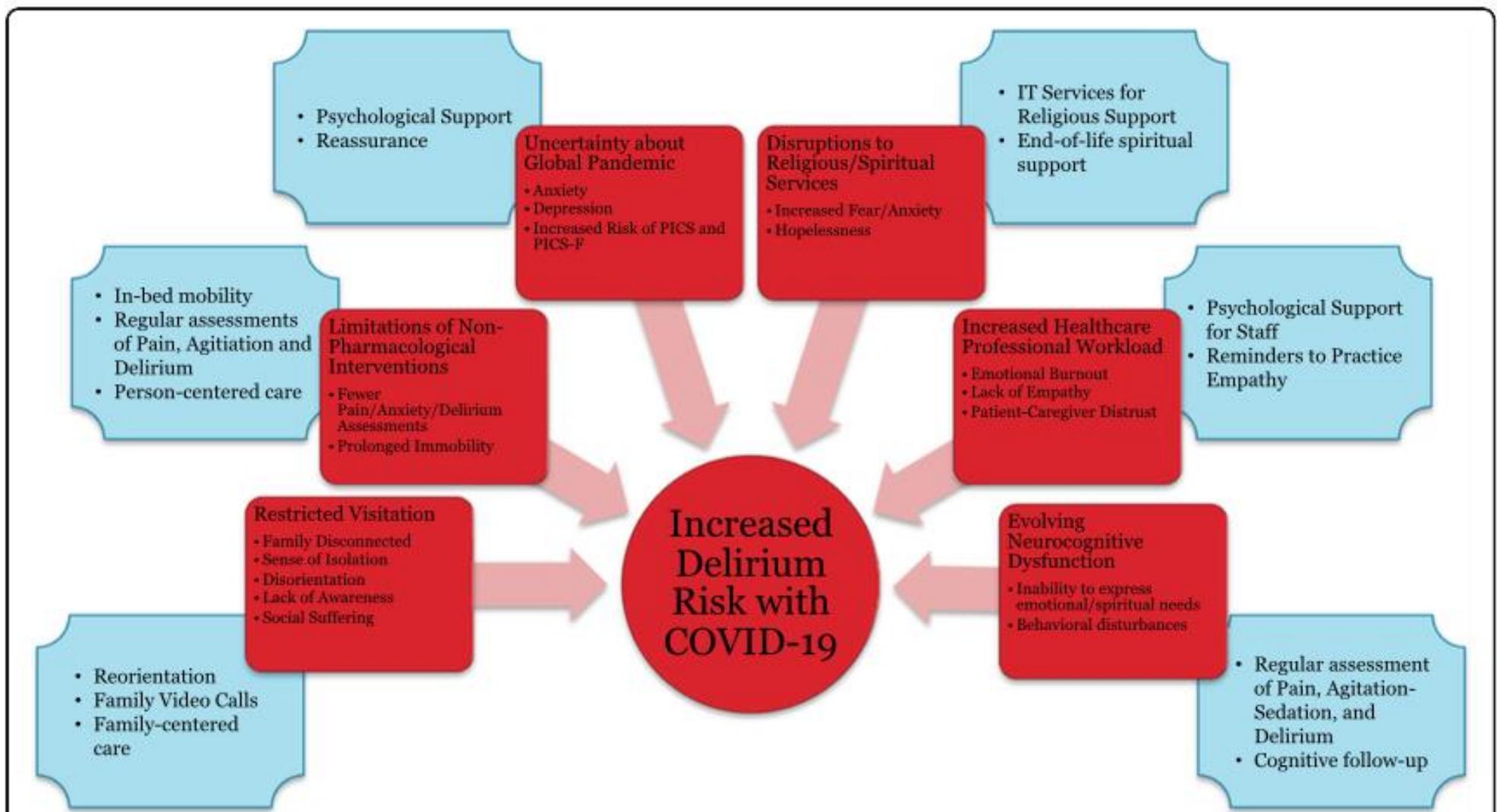
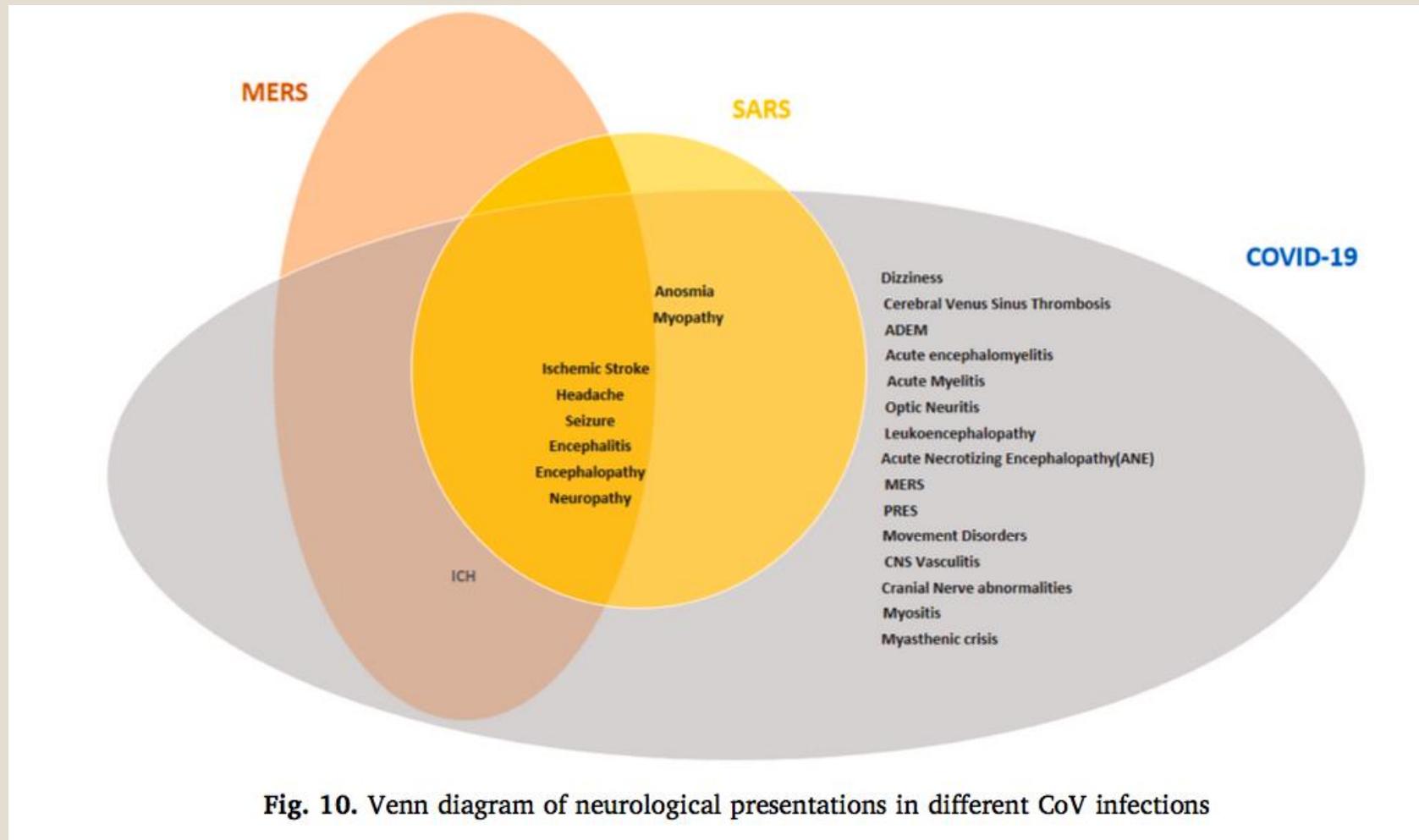


Fig. 1 Potential factors contributing to ICU delirium during the SARS-CoV-2 pandemic

COMPLICANZE NEUROLOGICHE: SARS-COV-1, MERS, SARS-COV-2



SARS-CoV-1

Table 1
Neurological Complications Reported During and After SARS-CoV-1 Infection.

No.	Neurological Symptom	Ref. No.	No. of patients	Mean Age of the patients (Range)	Notes
Symptoms related to CNS					
1	Ischemic stroke	[21] →	5 Patients 3F 2M	57.6(39–68)	Large artery ischemic stroke especially in critically ill patients.
2	Headache	[22]	F	62	
3	Seizure	[23]	F	32	CSF positive for SARS-CoV-1
4	Encephalitis	[24]	M	39	Autopsy tissue from the patient revealed neuronal necrosis, glial cell hyperplasia, and infiltration of monocytes and T cells.
Symptoms related to peripheral nervous system (PNS)					
5	Guillain-Barré syndrome (GBS)	[25] →	3F	47(42–51)	Both acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN)
6	Critical illness polyneuropathy	[26]	F	51	
	Smell impairment	[27]	F	27	
Symptoms related Skeletal Muscle injury					
7	Myopathy	[28] → [25],	5 M	54.8(31–81)	Leung TW et al. [28] study was a post-mortem study, steroid-induced myopathy suggested for these patients.(4 cases)

Abbreviation: M: Male, F: Female

MERS

Table 2
Neurological Complications Reported During and After MERS-CoV Infection.

No.	Neurological Symptom	Ref.	No. of patients	Mean Age of the patients (Range)	Notes
Symptoms related to CNS					
1	Ischemic stroke	[33]	2M	65.6(57–74)	
2	Intracranial hemorrhage (ICH)	[34], [35]	2F	38(34–42)	ICH in one of the patients was related to DIC and thrombocytopenia but the other patient had normal coagulation at the time of ICH.
3	Headache	[32]	9 (12.9%)	NR	
4	Seizure	[32]	6(8.6%)	NR	
5	Confusion	[32]	18 (25.7)	NR	
6	Encephalitis	[33]	M	45	CSF: Not significant
7	Bickerstaff's encephalitis overlapping with GBS	[36]	M	55	
Symptoms related to Peripheral nervous system (PNS)					
8	Guillain-Barré syndrome (GBS)	[34], [36]	4 patients 2M 2F	38.7(28–46)	

Abbreviation: M: Male, F: Female

SARS-CoV-2 (1)

Table 3
CNS Complications Reported During and After SARS-CoV-2 Infection.

No.	Neurological Symptom	Ref. No.	No. of patients	Mean Age of the patients(Range)	Notes
Headache and dizziness					
1	Headache	[38] [39] [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], 56, [57], [58], [59], [60] [61],[62], [63] [64] [65] [66], [67], [68], [69] [70], [178]	2073	NR in all articles.	
2	34 Articles Dizziness	[39], [43], [47], [48], [57], [60], [62], [69], [70], [71], [72]	173	NR in all articles.	Kong Z et al. [72] reported a 53 Y/O F with dizziness as the first presentation of COVID-19.
Cerebrovascular events					
3	Ischemic Stroke	[39], [57], [58], [60], [63], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98], [99], [100], [101], [102], [178], [192]	363	NR in all articles.	In large population studies ischemic stroke was reported in 1% [77] to 2.5% [84] of patients. Young adult patients without any past medical history [80] and patients with large-vessel stroke were reported. [80,85,95] One 38 Y/O F patient with stroke and CADASIL was reported. [89] A 67 Y/O M simultaneous cerebral infarcts in multiple arterial territories were reported. [91]
4	TIA	[58], [75], [94]	7	NR in all articles.	
5	3 Articles Cerebral Hemorrhage	[39], [57], [58], [60], [63], [75] [86], [92], [98], [99], [100], [101], [106], [107], [108], [109], [110], [111], [112],	61	NR in all articles.	Muhammad S et al. [107] reported a 60 Y/O F with aneurysm and ICH.
6	19 Articles Cerebral Venous Sinus Thrombosis	[99], [101], [102], [114], [115], [116], [117], [118], [192]	13	NR in all articles.	Ghosh R, et al. [111], reported a 19 Y/O F with Moyamoya Angiopathy and ICH. Malentacchi M et al. [102] reported 81 Y/O M with both arterial and venous thrombosis.
Acute demyelination					
7	Acute disseminated encephalomyelitis (ADEM)	[120], [121], [122], [123]	4	61(51-71)	Reichard RR et al. [122], study reported post-mortem examinations of a 71 Y/O M which revealed ADEM-like appearance at the brain biopsy.
8	4 Articles Acute Myelitis	[125], [126], [127], [128], [129]	5	55.6(22-69)	In one of these patients [125] CSF or MRI exam was not performed.
	5 Articles		3M 2F		Sotoca J et al. [127], reported 69 y/o F acute necrotizing myelitis.
9	Optic Neuritis	[60]	1	NR	Giorgianni A, et al. [128] reported a 22 Y/O F with transient acute-onset tetra paresis with normal MRI and CSF exam.
10	1 Article Acute encephalomyelitis	[132], [179] [187] [196]	4	21-54	Zoghi A et al. [132], reported 21 Y/O M suspicious to ADEM or neuromyelitis-optica spectrum disorder.
	4 Articles		2M 2F		Zanin L, et al. [179] reported a 54 Y/O F with seizure and brain and spine demyelinating lesions. Brun G et al. [187] reported a 54 Y/O F with Multiple supra-tentorial punctiform and tumefactive lesions involving the white matter bilaterally.

(continued on next page)

SARS-CoV-2 (2)

Table 3 (continued)

No.	Neurological Symptom	Ref. No.	No. of patients	Mean Age of the patients(Range)	Notes
					Demirci Oltuoglu G et al. [196] reported a 48 Y/O M with Acute encephalomyelitis and positive CSF for SARS-CoV2
	Impaired consciousness, encephalopathy and encephalitis				
11	Decreased level of consciousness And Encephalopathy	[39], [40], [57], [58] [60], [62] [88], [96], [98], [100], [101], [133], [135], [136] [137], [138], [139] [140], [141] [178] [184] [189] [195] [197]	4,54	NR in all articles.	Yin R et al. [133] reported a 64 Y/O M with altered consciousness and Psychiatric symptoms, his brain CT scan was Normal.
	22 Articles				Farhadian S et al. [138], reported a 78 Y/O F with acute encephalopathy and elevated CSF inflammatory markers.
					Hosseini AA et al. [139], reported 2 patients (46 Y/O, 79 Y/O) F with Delirium as a presenting feature in COVID-19, neuro-invasion or autoimmune encephalopathy was suggested as the cause.
12	Leukoencephalopathy	[144], [145] [188]	18	NR in all articles.	Kulick-Soper CV, et al. [189] reported a 54 Y/O F with bilateral globus pallidus lesions and possibility of hypoxic brain damage. Radmanesh A et al. [145] reported 4 patients with leukoencephalopathy one patient with micro-hemorrhages and six patients with both presentations.
13	3Articles Acute Necrotizing Encephalopathy(ANE)	[146] [147], [148], [149] [178] [193]	8	NR in all articles.	Virhammar J, et al. [146], reported 55 Y/O F with ANE with abnormal CSF.
	6 Articles				Radmanesh A et al. [147], reported 50 Y/O M delayed post-hypoxic necrotizing leukoencephalopathy.
14	Encephalitis	[60], [98], [100], [150], [151], [151], [152], [153], [154], [155], [156], [157], [158]	22	NR in all articles.	Dixon L et al. [149] reported ANE in a 59 Y/O F with history of aplastic anemia who died despite steroid therapy. Wong PF et al. [151], reported a 40 Y/O M Rhombencephalitis.
	13 Articles				Pilotto A et al. [152], a 60 y/o patient with steroid responsive encephalitis.
15	Mild encephalitis/encephalopathy with a Reversible Splenic Lesion(MERS)	[160]	1	75	Efe IE et al. [157], reported a 35 Y/O F with encephalitis mimicking glial tumor.
16	1 Article Posterior reversible encephalopathy syndrome (PRES).	[58], [101], [161], [162], [163] [164],[165], [190]	10	NR in all articles.	Franceschi AM et al. [161], reported 2 patients with hemorrhagic PRES.
	8 Articles				Kaya Y et al. [162], reported a 38 M with cortical blindness PRES like syndrome.
					Coolen T et al. [190]performed early postmortem brain MRI in patients who died from COVID-19 complications.
	Seizure				
17	Seizure	[39], [58], [60], [63], [101], [150], [166], [167], [168], [169], [170], [171], [172], [173], [174], [175] [176] [177], [178], [179]	48	NR in all articles.	Somani S et al. [166], Balloy G, et al. [167] and), Le Guennec L et al. [172] reported 4 patients with status epilepticus.
	20 Articles				Logmin K et al. [171], reported a 70 Y/O patient with non-epileptic seizures.

(continued on next page)

SARS-CoV-2 (3)

Table 3 (continued)

No.	Neurological Symptom	Ref. No.	No. of patients	Mean Age of the patients(Range)	Notes
					Elgamasy S et al. [174] reported 73 Y/O F with focal epilepsy.
					Vollono C et al. [175] reported a case of focal status epilepticus from left fronto-centro-temporal area(MRI showed extensive gliosis and atrophy at that site due to previous herpes encephalitis.)
					Scullen T et al. [178], reported a case of non-convulsive status epilepticus.
	Movement disorders				
18	Generalized Myoclonus, Hypokinetic-rigid syndrome	[182], [183]	4 3M 1F	71.25(58-88)	
	2 Articles				
	CNS Vasculitis				
19	CNS Vasculitis	[98] [185],	2	NR in all articles.	
	2 Articles				
	Cranial Nerve abnormalities				
20	Anosmia	[39], [56], [57], [58], [62], [69], [101], [182], [198], [199], [200], [201], [202], [203], [204], [205], [206], [61], [207], [208], [209], [210], [211], [212], [213] [214],	3730	NR in all articles.	Mermelstein S [202] a 27 Y/O neurology registrar, reported her symptoms and anosmia after COVID-19.
	28 Articles				
21	Ageusia	[39], [56], [57], [58], [61], [62], [69], [200], [204], [205], [206], [214]	2590	NR in all articles.	
	14 Articles				
22	Impaired Vision	[39], [57], [204]	12	NR in all articles.	
	3 Articles				

Abbreviation: M: Male, F: Female, NR: Not reported.

Caso clinico

Pz di 70 anni accede al PS il 28 *Marzo* lamentando **astenia**, **parestesia** a mani e piedi che progrediscono in 1 giorno.

Il 4 *Marzo* aveva sviluppato febbre (TC = 38,5° C) e tosse secca.

Il giorno dopo ha eseguito il tampone nasofaringeo per SARS-Cov-2-RNA su RT-PCR risultato: **POSITIVO**.

In pochi giorni i sintomi di COVID-19 si sono risolti.

(L'indagine epidemiologica aveva rivelato una precedente visita ospedaliera ad un ricoverato in un'area ad alta incidenza di COVID-19 (Piacenza, Italia) il 28-29 febbraio.)

All'accesso la TC era 36,5° C, la satO₂ 98% in AA.

L'emogas arterioso ha mostrato pO₂ = 76 mmHg con il normale rapporto P/F (= 363).

Gli esami ematochimici hanno evidenziato:

- un lieve aumento dei globuli bianchi (10,41*10⁹/L, normale = 4-10*10⁹/L)
- 8,15*10⁹/L neutrofili (normale = 2-8*10⁹/L)
- Linfociti nella norma.

Nella **NORMA**: D-dimero, CPK, glicemia, funzionalità epatica, renale, proteina c-reattiva, il tasso di sedimentazione degli eritrociti, i livelli di folato e vitamina B12.

TAC ad alta risoluzione del torace ha rivelato alcune piccole aree di "vetro smerigliato" in entrambi i polmoni.

Ripetuto tampone nasofaringeo per la SARS-Cov-2-RNA: **NEGATIVO**

Mycoplasma pneumoniae e citomegalovirus (CMV) (IgM e IgG)
Legionella pneumophila
Streptococcus Pneumoniae: uricolture

}
NEGATIVI

EON: ipostenia degli arti superiori e inferiori simmetrica moderata (grado 4/5 del Consiglio di Ricerca Medica), perdita dei riflessi osteo-tendinei profondi, preservata la sensibilità esterocettiva (tattile e dolorifica)

Il *31 marzo* è stata eseguita una puntura lombare. L'analisi del liquido cerebrospinale (CSF) ha rivelato una leggera dissociazione albumino-citologica (proteine del CSF = 48 mg/dL, normale = 0-40 mg/dL, globuli bianchi = $1 \cdot 10^6/L$, normale = $0-8 \cdot 10^6/L$).

Effettuato test microbiologico sul CSF: NEGATIVO (herpes simplex virus, varicella zoster virus, Epstein-Bar virus, CMV, HIV-1, Borrelia Burgdorferi IgM e IgG).

Neurofisiologia coerente con **sindrome di Guillain Barrè (GBS)**.

È stato avviato uno studio con 400 mg/die di immunoglobulina endovenosa (Ivig) per 5 giorni.

Il *1 aprile* la paziente è stata intubata ed è stata applicata la ventilazione meccanica, a causa di insufficienza respiratoria dovuta al peggioramento della debolezza muscolare.

Sindrome di Guillain Barrè (GBS)



Fig. 1 Timeline of clinical events and diagnostic investigations. *COVID-19* coronavirus disease-2019, *GBS* Guillain-Barré syndrome, *LP* lumbar puncture, *IVIg* intravenous immunoglobulin, *MV* mechanical ventilation

Si può ipotizzare quindi un'**associazione** tra la poliradicolopatia acuta e l'infezione da Covid-19.

LIMITI DELLO STUDIO:

- sensibilità subottimale riportata della RT-PCR per tampone a causa di errore di laboratorio o materiale virale insufficiente (no ricerca IgM e IgG COVID-19)
- Non eseguito test anticorpale antiganglioside per identificare i target specifici del processo autoimmune GBS
- Non è stato eseguito uno screening paraneoplastico/autoimmune completo nella fase acuta (ANCA)
- Altri agenti infettivi meno comuni (ad es. i virus del Nilo occidentale e della Toscana), non testati ma endemici nell'Italia settentrionale non sono stati ricercati

Non si poteva quindi escludere la possibilità di una poliradicolopatia autoimmune o para-neoplastica che imitasse la GBS.

Grazie per l'attenzione