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LETTER TO THE EDITORS

Mixed central and peripheral nervous system disorders in severe SARS-CoV-2 infection

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Dear Sirs,

We report four cases of severe COVID-19 in male patients aged 50–70 with the combination of central and peripheral nervous system disorders occurring unexpectedly late after the first symptoms. Patients had comorbidities and were admitted for acute respiratory distress syndrome due to a proven SARS-CoV-2 infection. All required mechanical ventilation, among whom one needed an extracorporeal membrane oxygenation support.

Several acute neurological syndromes have been associated with SARS-CoV-2 infection, including anosmia and ageusia [1, 2], meningoencephalitis [3, 4], acute hemorrhagic necrotizing encephalopathy [5], axonal or demyelinating polyradiculoneuropathy [6–8], polyneuritis cranialis [8]. Like in most of the viral infections that involve nervous system, these manifestations occurred within the first ten days after infectious symptoms. Further away from the onset of the disease, when sedation and neuromuscular blocker were withheld, 67% of the patients with severe COVID-19 develop encephalopathy including prominent agitation, confusion and corticospinal tract signs [9].

In our cases neurological manifestations were detected after mechanical ventilation weaning and extubation (Fig. 1). They consisted of miscellaneous symptoms such as confusion, cognitive dysfunction (memory deficit, frontal syndrome), psychiatric disorders (paranoid delusion, hallucinations), weakness, pyramidal signs, dysautonomia, swallowing dysfunction, vertical supranuclear eye palsy, upper limbs myoclonus, fasciculation and focal muscle atrophy (Table 1). To note, before admission to intensive care unit, patients had no neurological symptom, except for anosmia or ageusia in two of them. One patient had a small acute sub-cortical ischemic stroke on brain MRI. Cerebrospinal fluid (CSF) analysis showed a normal cell count and a moderate increase of protein level in the up to 80 mg/L in two cases. RT-PCR and IgM for SARS-CoV-2 in the CSF were negative in all patients. On EEG, non-rhythmic frontal slow waves were observed in two patients. Three patients had electrophysiological features of acute motor demyelinating polyradiculoneuropathy with delayed distal latencies and F-waves, slowed conduction velocities and conduction blocks (Supplementary Table). The remaining patient had lower motor neuron features in both the upper and lower limbs. Two patients had an additional decrease of sensorimotor potential amplitude compatible with a critical illness neuropathy. Swallowing and eye movement improved within the first week. Given the persistent muscle weakness and electromyographic features suggesting a post-infectious mechanism, an immunoglobulin therapy was introduced for 5 days. Psychiatric symptoms, cognitive impairment and dysautonomia improved thereafter, but myoclonus and motor weakness of the upper limbs persisted 3 weeks after

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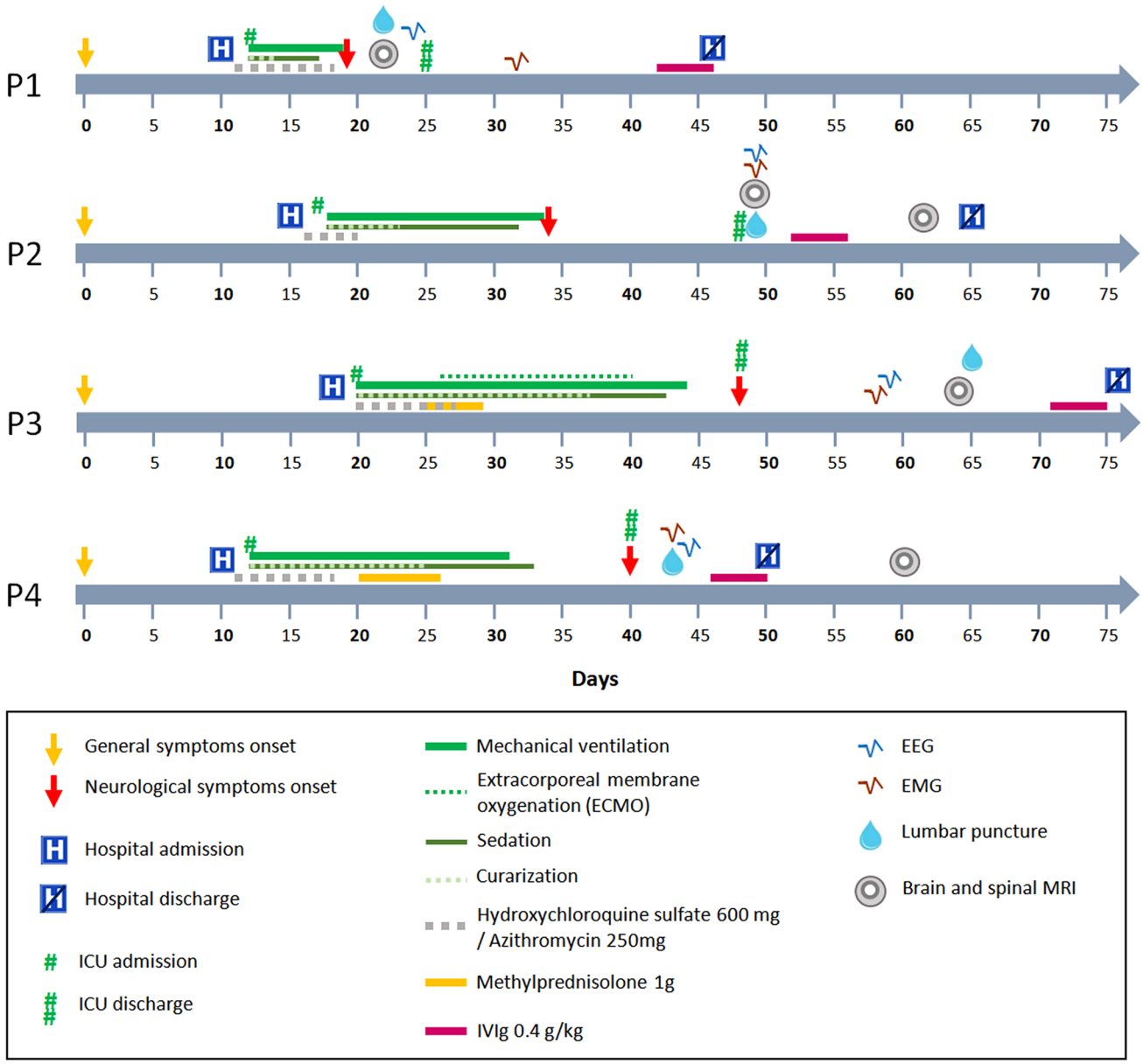

Fig. 1 Timelines showing general and neurological symptoms onset, timing of hospital admission and discharge, timing of ICU admission and discharge, and paraclinical examinations and treatments. *EEG,* electroencephalogram; *EMG* electromyogram; *ICU* intensive care unit; *IVIg* intravenous immunoglobulin; *MRI* magnetic resonance imagery. P1: Patient 1 (M, 62 y.o), P2: Patient 2 (M, 72 y.o), P3: Patient 3 (M, 50 y.o), P4: Patient 4 (M, 66 y.o). For P2, cerebral and spinal MRI were performed at two different dates (days 49 and 62, respectively)

discharge. Three patients required prolonged rehabilitation in a specialized center.

We describe here delayed mixed central and peripheral disorders as a complication of severe COVID-19. It combines acute encephalopathy and motor demyelinating polyradiculoneuropathy or diffuse lower motor neuron involvement. Persistent cognitive and motor deficit might result from a critical illness, but neurological features differ from critical illness-related encephalopathy and neuropathy. Critical illness-related neuropathy is characterized by a bilateral, symmetric, axonal sensorimotor polyneuropathy resulting in an areflexic tetraplegia, without dysautonomia or cranial nerves palsy. In our patients, clinical and neurophysiological features of peripheral nervous system involvement could partly reflect critical illness neuropathy but most of them are not expected in this context and are thus more likely linked to COVID-19. Abnormal eye movement, swallowing dysfunction and action myoclonus are unusual in

Table 1 Characteristics and management of severe COVID-19 patients presenting with mixed central and peripheral neurological manifestations

ID age sex	Comorbidities	Delay between inaugural symptoms and admission to:	Inaugural symptoms	Neurologic features at evaluation[a]	MRI	EEG	EMG (main features)	SARS-CoV-2 RT-PCR Serology[a]	CSF[b] WCC/ Protein mg/L SARS-CoV-2 tests	Severity of ARDS[c] and medical care
1, 62, M	Hypertension, diabetes mellitus	Hospital: 10 days, ICU: 12 days	Fever, cough, ageusia, dyspnea	Confusion, dysexecutive syndrome, memory deficit, swallowing disorders, left facial palsy, right UL weakness (2/5) with bilateral atrophy of the first palmar interosseous, left UL and LL strength 4/5, ataxia, postural and action myoclonus, lower limb areflexia, upper limb hyperreflexia, dysautonomia[d], GSC 15, mRS 5 ([a]day 21)	Recent ischemic stroke in right middle cerebral artery territory (Brain MRI) Normal spinal cord MRI	Global slowing (5–6 Hz) Bilateral and frontal, disphasic, non-periodic slow activity (2 Hz)	Demyelinating asymmetric motor polyradiculo neuropathy and moderate axonal sensorimotor neuropathy of the four limbs	Positive RT-PCR in nasopharyngeal swab, + IgM, + IgG in plasma ([a]day 13)	0 / 45 negative RT-PCR,- IgM, + IgG, No intrathecal synthesis	Mild ARDS[e] Hydroxychloroquine sulfate 600 mg Azithromycin 250 mg, ICU, V, no PP, IVIg 0.4 g/kg, Rehabilitation center after 36 days, mRS 2

Table 1 (continued)

ID age sex	Comorbidities	Delay between inaugural symptoms and admission to:	Inaugural symptoms	Neurologic features at evaluation[a]	MRI	EEG	EMG (main features)	SARS-CoV-2 RT-PCR Serology[a]	CSF[b] WCC/ Protein mg/L SARS-CoV-2 tests	Severity of ARDS[c] and medical care
2, 72, M	Hypertension, Diabetes mellitus, Obesity, (BMI = 31.5), Urothelial carcinoma in remission	Hospital:15 days, ICU: 17 days	Fever, cough, dyspnea	Confusion, paranoid delusion, visual and auditory hallucinations, frontal syndrome, memory deficit, swallowing disorders, tetraparesis (UL and LL strength 2/5), ataxia, UL rest, postural and action myoclonus, slowing of eye movement saccades, four limbs hyperreflexia and neurogenic pain, dysautonomia[d], GSC 14, mRS 5 ([a]day 44)	Normal brain and spinal cord MRI	Global slowing (5–6 Hz)	Demyelinating motor polyradiculoneuropathy and moderate to severe axonal sensorimotor neuropathy of the four limbs	Positive RT-PCR in nasopharyngeal swab, + IgM,—IgG in plasma, ([a]day 18)	0 / 74, negative RT-PCR,—IgM, + IgG, No intrathecal synthesis	Mild to moderate ARDS[e] Hydroxychloroquine sulfate 600 mg, Azithromycin 250 mg QT prolongation, Pregabalin 300 mg per day, ICU, V, no PP IVIg 0.4 g/kg, Rehabilitation center after 50 days, mRS 4

Table 1 (continued)

ID age sex	Comorbidities	Delay between inaugural symptoms and admission to:	Inaugural symptoms	Neurologic features at evaluation[a]	MRI	EEG	EMG (main features)	SARS-CoV-2 RT-PCR Serology[a]	CSF[b] WCC/ Protein mg/L SARS-CoV-2 tests	Severity of ARDS[c] and medical care
3, 50, M	Diabetes mellitus	Hospital: 18 days, ICU:20 days	Cough, dyspnea	Confusion, paranoid delusion, frontal syndrome, memory deficit, swallowing disorders, tetraparesis, (UL strength 2/5 and LL strength 3/5), bilateral atrophy of the first palmar interosseous, ataxia, UL rest, postural and action myoclonus, slowing of eye movement saccades, four limbs hyperreflexia, bilateral ankle clonus, dysautonomia[d], GSC 14, mRS 5 ([a]day 54)	Normal brain and spinal cord MRI	Posterior and metric global slowing (6 Hz) bilateral frontal paroxysmal slow, delta waves	Lower motor neuron involvement with denervation of the four limbs, normal motor evoked potential amplitude	Positive RT-PCR in nasopharyngeal swab + IgM, + IgG in plasma ([a]day 19)	5 / 81 negative RT-PCR— IgM, + IgG, No intrathecal synthesis	Moderate to severe ARDS[e], Hydroxychloroquine sulfate 600 mg, Azithromycin 250 mg Methylprednisolone 1 g, ICU, ECMO, V, PP (× 1), IVIg 0.4 g/kg, Rehabilitation center after 76 days, mRS 4

Table 1 (continued)

ID age sex	Comorbidities	Delay between inaugural symptoms and admission to:	Inaugural symptoms	Neurologic features at evaluation[a]	MRI	EEG	EMG (main features)	SARS-CoV-2 RT-PCR Serology[a]	CSF[b] WCC/ Protein mg/L SARS-CoV-2 tests	Severity of ARDS[c] and medical care
4, 66, M	Obstructive sleep apnea syndrome	Hospital: 10 days, ICU: 12 days	Cough, Dyspnea, Anosmia, Diarrhea	Confusion, paranoid delusion, visual hallucinations, frontal syndrome, memory deficit, tetraparesis (UL and LL strength 3/5), ataxia, UL postural and action myoclonus, UL hyperreflexia, LL areflexia, dysautonomia[d], GSC 15, mRS 4 ([a]day 42)	Normal brain and spinal cord MRI	Normal	Demyelinating motor polyradiculo neuropathy of the four limbs	Positive RT-PCR in nasopharyngeal swab,—IgM, + IgG in plasma ([a]day 10)	1 / 22, negative RT-PCR,- IgM, + IgG, No intrathecal synthesis	Mild to severe ARDS[e,] Hydroxychloroquine sulfate 600 mg, Azithromycin 250 mg (day 11–18) Methylprednisolone 1 g (day 20 to 26) ICU, V, PP (×6) IVIg 0.4 g/kg, Discharged at home after 40 days mRS 2

BMI body mass index; *CSF* cerebrospinal fluid; *ECMO* extracorporeal membrane oxygenation; *EEG* electroencephalogram; *EMG* electromyogram; *GSC* Glasgow scale; *ICU* intensive care unit; *IgM* immunoglobulin M; *IgG* immunoglobulin G; *IVIg* intravenous immunoglobulin; *LL* lower limb; *UL* upper limb; *MRI* magnetic resonance imaging; mRS, modified Rankin Scale; *NA* not applicable; *PP* prone position; *RT-PCR* real-time polymerase chain reaction; *V* mechanical ventilation; *WCC* white cell count (μL)

[a]Time after inaugural symptoms

[b]Cerebrospinal fluid analysis was performed at the time of neurological examination

[c]Severe Acute Respiratory Distress Syndrome (ARDS): PaO2/FiO2 < 100; moderate *ARDS*: PaO2/FiO2 < 200; mild, *ARDS*: PaO2/FiO2 < 300; *PaO2/FiO2* ratio was calculated using the arterial Pressure of oxygen (PaO2) and the fraction of inspired oxygen (FiO2) in mechanical ventilated patients

[d]Dysautonomia: orthostatic hypotension, constipation

[e]Patient 1 (PaO2/FiO2): day 1: 208, day 2: 280, day 3: 240, day 7: 218; Patient 2 (PaO2/FiO2): day 1: 224, day 2: 220, day 3: 204, day 7: 174; Patient 3 (PaO2/FiO2): day 1: 140, day 2: 203, day 3: 78, day 7: 44; Patient 4 (PaO2/FiO2): day 1: 75, day 2: 234, day 3: 162, day 7: 69

mRS was defined as: **0**: No symptoms at all; **1**:No significant disability despite symptoms; able to carry out all usual duties and activities; **2**:Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; **3**:Moderate disability; requiring some help, but able to walk without assistance; **4**:Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; **5**:Severe disability; bedridden, incontinent and requiring constant nursing care and attention

critical illness-related encephalopathy and might rather result from COVID19-related brainstem dysfunction in our patients.

Our study suggests a wider spectrum than previously reported of neurological manifestations associated with COVID-19 and further suggests that patients with severe forms of COVID-19 should be systematically screened for neurological complications.

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Consent for publication Patient's consent has been obtained.

Conflicts of interest Dr. Chaumont reports having received travel grant from PEPS development, Roche and Pfizer. Dr. Roze reports served on scientific advisory boards for Orkyn, Aguettant, Merz-Pharma; received honoraria for speeches from Orkyn, Aguettant, Merz-Pharma, Medday-Pharma, Everpharma, International Parkinson and Movement disorders Society; received research support from Merz-Pharma, Orkyn, Aguettant, Elivie, Ipsen, Everpharma, Fondation Desmarest, AMADYS, Fonds de Dotation Brou de Laurière, Agence Nationale de la Recherche; received travel grant from Vitalair, PEPS development, Aguettant, Merz-Pharma, Ipsen, Merck, Orkyn, Elivie, Adelia Medical, Dystonia Medical Research Foundation, International Parkinson and Movement disorders Society, European Academy of Neurology, International Association of Parkinsonism and Related Disorders. Dr. Couratier reports having received travel grant from Allergan, Novartis, Esai, UCB, Medtronic, Merck Serono, Biogen, LFB, Teva, Icomed, GSK, Genzyme, Aguettant, Cyberonics and Merz-Pharma. Dr. Lannuzel reports having received research support from France Parkinson, PSP France, Agence Nationale de la Recherche, Fonds Européen de DEveloppement Regional, French Ministry of Health, University Hospital of Guadeloupe, received honoraria for a speech from Association des Neurologues du Québec; received travel grant from Vitalair, PEPS development, Merz-Pharma, International Parkinson and Movement disorders Society. Dr. San-Galli, Dr. Martino, Dr. Carles, and Dr. Joguet report no disclosures.

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