Movement disorders as a new neurological clinical picture in severe SARS-CoV-2 infection

P. Cuhna[a], B. Herlin[a], K. Vassilev[a], A. Kas[b,c,d], S. Lehericy[c,d,e], Y. Worbe[c,f], E. Apartis[c,d,f], M. Vidailhet[c,d,g] and S. Dupont[a,c,d,h]

[a]*Rehabilitation Unit, Pitié-Salpêtrière Hospital, AP-HP, Paris,* [b]*Nuclear Medicine Unit, Pitié-Salpêtrière Hospital, AP-HP, Paris,* [c]*Université Paris Sorbonne, Paris,* [d]*Institute of Brain and Spinal Cord, Paris,* [e]*Neuroradiology Unit, Pitié-Salpêtrière Hospital, AP-HP, Paris,* [f]*Neurophysiology Unit, Saint Antoine Hospital, AP-HP, Paris,* [g]*Movement Disorders Unit, Pitié-Salpêtrière Hospital, AP-HP, Paris, and* [h]*Epilepsy Unit, Pitié-Salpêtrière Hospital, AP-HP, Paris, France*

Correspondence: S. Dupont, Rehabilitation Unit, Pitié-Salpêtrière Hospital, AP-HP, Paris, France (tel.: (33) 1 42 160301; fax: (33) 1 42 16 0638; e-mail: sophie.dupont@aphp.fr).

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New forms of neurological complications of severe SARS-CoV-2 infection have been described, mainly including encephalopathy, agitation and confusion [1]. Only one publication reveals the emergence of *de novo* myoclonus in three patients [2], with most publications reporting the aggravation of pre-existing abnormal movements disorders. Here, we identified and characterized in depth clinically a new type of delayed onset movement disorder in five patients who were admitted to the Assistance Publique – Hôpitaux de Paris intensive care unit (ICU) for severe SARS-CoV-2 infection. All patients underwent intubation and mechanical ventilation.

Abnormal movements developed 23 ± 7 days (mean ± SD) after ICU discharge. Upper limb postural and action tremor was observed in four patients; one of them (patient 2) also had irregular orthostatic tremor and one patient (patient 4) had bilateral upper limb jerky/myoclonic abnormal movements at rest and during posture and action (Table 1). Associated signs included a moderate proximal motor deficit attributed to a critical illness myopathy in four patients and a mild hemiparesis attributed to a critical illness neuropathy confirmed by electroneuromyography in one patient.

Electrophysiological exploration of the movement disorders was performed in patients 2 and 4 and recorded myoclonic jerks of short duration (40–60 ms) that were synchronous among the electromyography (EMG) traces, associated with post-myoclonic inhibition period in one patient and with jerks of longer duration (50–100 ms) and increased long loop C-reflex with latency of 50 ms recorded from thenar muscles in the second. Overall, the recordings supported a mixed cortical–subcortical pattern of myoclonic jerks (Fig. 1).

Magnetic resonance imaging (MRI) (3 T) performed in all patients showed in four patients microbleeds which are non-specific injuries associated with the resuscitation setting [3] and a bilateral frontotemporal hypoperfusion in one patient. Neuromelanin-sensitive MRI showed that the dorsal nigral hyperintensity sign was bilaterally present in four patients but was asymmetrical and only present in one hemisphere in patient 1. Single photon emission computed tomography (SPECT) with ^{123}I-FP-CIT (DaTScan) performed in four patients showed no significant decrease of striatal uptake in any of them.

Several pathophysiological mechanisms may be hypothesized here: (i) direct central nervous system damage by SARS-CoV-2 or of post infectious/immune-mediated origin, (ii) metabolic (renal failure) and post-hypoxic myoclonus [4,5] no hypothesis is exclusive of the others.

For the first hypothesis, SARS-CoV-2 is known to enter the brain [5], where it can bind to the enzyme angiotensin-converting enzyme 2 and cause neuronal death. In line with that, we observed MRI abnormalities such as alterations of nigrosomes (substantia nigra) and frontotemporal hypoperfusion on MRI perfusion sequence that could be directly or indirectly related to SARS-CoV-2 [4]. The delayed onset (3 weeks after ICU discharge) of these movement disorders can also be in favor of SARS-COV-2 related immune implication. Alternatively, cortical and subcortical myoclonus may be related to post-infectious myoclonus, although this hypothesis is less likely in the absence of opsoclonus or ataxia. Finally, electrophysiological exploration documented cortical (abnormal long loop C-reflex) and subcortical (long duration bursts) myoclonus. We thus cannot exclude a combination of chronic post-hypoxic myoclonus with action and intention myoclonus of subcortical and cortical origin with possible additional metabolic origin in patient 4 with renal failure syndrome.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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Table 1 Clinical and radiological characteristics of five patients presenting with new onset movement disorder

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	51	67	34	66	48
Sex	Male	Male	Male	Female	Male
Medical history	Disc herniation	Hypertension, poliomyelitis	Hepatitis B healed, typhoid	Hypertension, nephroangio-sclerosis with severe renal insufficiency stage V, hepatitis B healed	Hypertension, obesity
Nasopharyngeal swabs for SARS-CoV-2 RNA	Positive	Positive	Positive	Positive	Positive
Delay between the onset of symptoms and the diagnosis of SARS-CoV-2, days	9	8	5	11	7
ICU					
Prone positioning	—	Yes	Yes	Yes	Yes
Extracorporeal membrane oxygenation procedure (ECMO), days	—	14	9	—	18
Tracheotomy, weeks	—	3	—	—	—
Average length of stay in ICU, days	12	23	25	19	34
Time to neurological presentation after extubation, days	17	31	14	29	24
Average weight loss, kg	5	6	15	6	16
Other complications of SARS-CoV-2 infection	Pneumopathy	Pneumopathy	Pneumopathy	Pneumopathy, worsening renal failure requiring dialysis, delirium after extubation requiring haloperidol medication that was rapidly discontinued	Pneumopathy
Neurological examination in rehabilitation unit					
Type of tremor	Action tremor predominant on the right hemibody	Postural and action tremor of upper and lower limbs + orthostatic tremor	Postural and action tremor of the upper limbs	Jerky tremor of the upper limbs	Postural and action tremor of the upper limb
Myoclonus	No	Cortical and subcortical	No	Cortical and subcortical	No
Pyramidal syndrome	No	No	No	No	No
Extrapyramidal syndrome	No	No	No	No	No
Motor deficit	Mild global proximal deficit predominating on the right side	Mild right hemiparesis	Mild global proximal deficit	Mild global proximal deficit	Mild proximal belt deficit
Critical illness neuropathy	Yes	No	No	No	No
Critical illness myopathy	Yes	No	Yes	Yes	Yes
Abnormal movement recording	—	Combination of cortical and subcortical myoclonus	—	Combination of cortical and subcortical myoclonus	—
MRI					
Standard MRI	Bilateral frontotemporal hypoperfusion	Corpus callosum microbleeds	Corpus callosum microbleeds	Deep and peripheral microbleeds	Corpus callosum microbleeds

(continued)

Table 1 *(Continued)*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Neuromelanin sequence	Loss of visibility of the nigrosomes	Normal	Normal	Normal	Normal
DaTScan	Normal	Normal	Normal	Normal	—

DaTScan, 123I[A1] -FP-CIT SPECT; ICU, intensive care unit; MRI, magnetic resonance imaging.

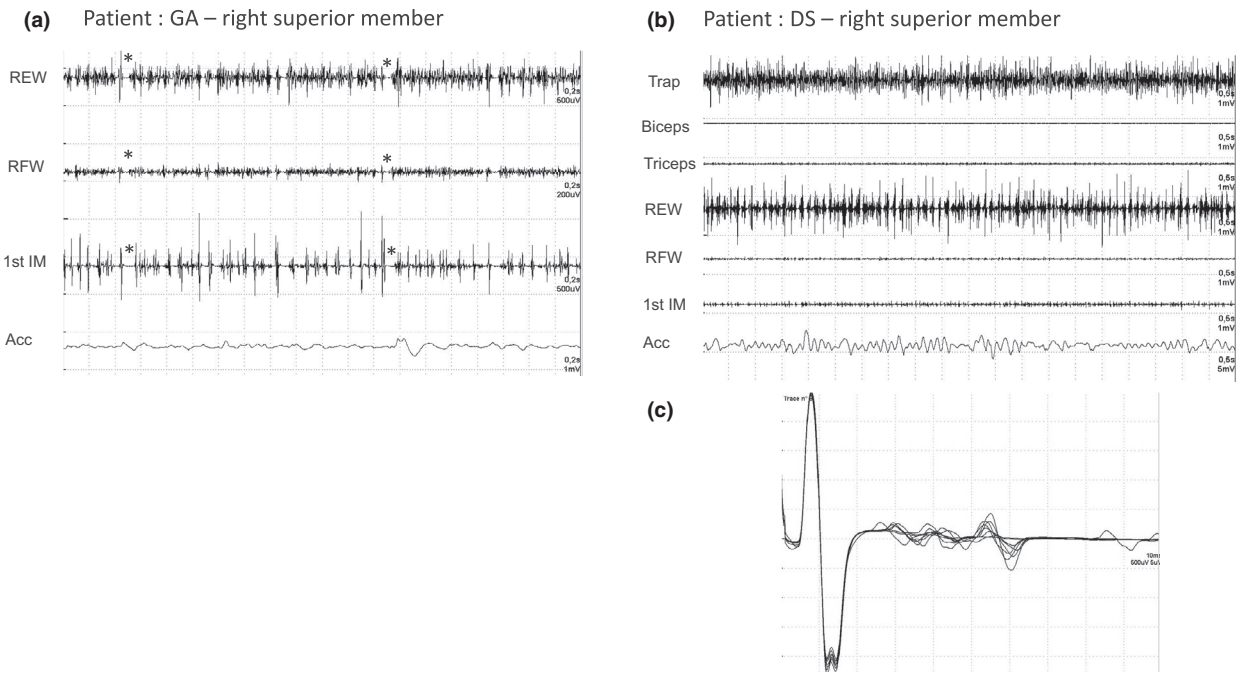

Figure 1 Myoclonus electrophysiology (patients 2 and 4). REW, radial extensor of wrist; RFW, radial flexor of wrist; 1st MI, first interossal muscle; Acc, accelerometer; Trap, trapezius muscle. (a) Surface EMG of right superior member, patient 2: REW, myoclonic bursts of 40–44 ms with 36–44 ms of post-myoclonic inhibition period (indicated with *); RFW, myoclonic bursts of 24 ms with 66 ms of post-myoclonic inhibition period (indicated with *); 1st MI, myoclonic bursts of 36 ms with 86 ms of post-myoclonic inhibition period (indicated with *). (b) Surface EMG of right superior member, patient 4: irregular myoclonic activity on the EMG of trapezius and REW with 70–94 ms of duration of myoclonic bursts. (c) Long loop C reflex with latency of 50 ms recorded from the thenar muscles of patient 4.