LETTER TO THE EDITOR

Severe COVID-19-related encephalitis can respond to immunotherapy

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We read with great interest the article of Ross W. Paterson and colleagues in *Brain* (Paterson *et al.*, 2020), in which they describe the emerging spectrum of coronavirus disease-2019 (COVID-19) neurological syndromes. This article provides major categories of COVID-19-related neurological syndromes, including patients with encephalitis, and reports corticosteroids and intravenous immunoglobulin response in some patients. Indeed, various COVID-19-related neurological syndromes have been reported since December 2019 (Filatov *et al.*, 2020; Helms *et al.*, 2020; Khoo *et al.*, 2020; Mao *et al.*, 2020; Moriguchi *et al.*, 2020; Oxley *et al.*, 2020; Poyiadji *et al.*, 2020). However, encephalitis has seldom been reported and the potential benefit of immunotherapy remains unclear (one out of two patients improved in Paterson *et al.*, 2020). Herein, we report a case series of five patients (from an observational cohort: the CoCo Neurosciences Study) with severe COVID-19-related encephalitis (impaired consciousness/unresponsive and mechanically ventilated) treated by plasma exchange (PLEX) and corticosteroids. The dramatic improvement in three out of five

patients reinforces the hypothesis of an immune-related mechanism, as evoked by Paterson and colleagues. Neurologists and intensivists should be aware that this life-threatening COVID-19 neurological syndrome has a potentially favourable outcome after immunotherapy, and should not motivate systematic limitation in active patient care.

Patients were aged between 37 and 77 years with COVID-19-related encephalitis presenting with altered consciousness, and were treated by PLEX and corticosteroids. They all fulfilled diagnosis criteria for possible immune encephalitis according to Graus *et al.* (2016). The clinical presentation and the time-course of the disease are summarized in Table 1, and complementary explorations findings are summarized in Table 2 (a detailed history is available for each patient in the Supplementary material).

Patients had no prior history of neurological disease. They were intubated and mechanically ventilated for COVID-19-related acute respiratory distress syndrome (ARDS). After sedation withdrawal (ranging from Day 12–30 from initiation), they presented severe and persistent consciousness disorder (comatose state or unresponsive wakefulness syndrome), three had oculomotor disturbances (Cases 1, 2 and 3) and one had peripheral symptoms attributed to Guillain-Barré syndrome (Case 3). CSF examinations were unremarkable except in one patient with albuminocytologic dissociation (Case 3), and one with mild pleocytosis (Case 4). Reverse transcription polymerase chain reaction (RT-PCR) assays of the CSF were negative for severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), as common viruses for all patients (Supplementary material). Onconeural antibodies were negative in serum and CSF. None of the patients had signs of thrombotic microangiopathy (no haemolysis, normal levels of ADAMTS13 activity and antigen). When performed, somatosensory evoked potentials showed bilateral presence of N20 (Cases 2, 3 and 4). EEGs showed unspecific slow-wave activity. Brain MRIs mostly showed bilateral hyperintense lesions in the deep and periventricular supratentorial white matter, either punctiform and slightly diffuse (Cases 1, 2 and 3) or diffuse and confluent (Cases 4 and 5), associated with lesions in the pons for two patients (Cases 1 and 2) (Supplementary Fig. 1).

All patients received immunotherapy combining corticosteroids infusions (1 g/day intravenous methylprednisolone for 5–10 days) and PLEX with albumin (5 to 10 sessions). It is worth noting that neurological impairment remained unchanged in all patients with severe consciousness disorder despite cessation of sedation for 9–33 days. Three patients (Cases 1, 2 and 3) showed dramatic neurological improvement few days after immunotherapy initiation (6, 2, and 7 days, respectively), with consciousness improvement allowing functional

communication. Two patients (Cases 4 and 5) showed no signs of consciousness improvement and died after discontinuation of life-sustaining therapies.

Relation between immunotherapy and clinical improvement

Although a neuro-invasive potential of SARS-CoV-2 is suspected—as for others coronaviruses—there are surprisingly few reports of COVID-19-associated encephalitis (Hanna Huang *et al.*, 2020; Le Guennec *et al.*, 2020; Moriguchi *et al.*, 2020; Paterson *et al.*, 2020). An immune-mediated mechanism has been proposed to explain coronaviruses-associated encephalitis (Weyhern *et al.*, 2020), and PLEX has shown promising results in a recent case series of COVID-19 mild meningoencephalitis (Dogan *et al.*, 2020).

Reports on patients with positive SARS-CoV-2 RT-PCR assay in the CSF are scarce (Hanna Huang *et al.*, 2020; Moriguchi *et al.*, 2020) and most patients had moderate acute cognitive impairment without pleocytosis (Helms *et al.*, 2020) or mildly elevated CSF cell counts (Bernard- Valnet *et al.*, n.d.). Likewise, Guillain-Barré and Miller Fisher syndromes, acute necrotizing haemorrhagic encephalopathy, and acute disseminated encephalomyelitis have also been described in COVID-19 patients, suggesting a host-immune response mechanism rather than a direct neuro-invasion of the SARS-Cov-2 (Gutiérrez-Ortiz *et al.*, 2020; Novi *et al.*, 2020; Toscano *et al.*, 2020). In the Paterson cohort, 10 patients were treated with corticosteroids, and three of these patients also received intravenous immunoglobulin; one made a full recovery, 10 of 12 made a partial recovery, and one patient died (Paterson *et al.*, 2020).

In our cases, the secondary neurological involvement (no prior neurological initial symptoms), associated with the MRI abnormalities and the absence of SARS-CoV-2 in the CSFs point towards a post-infectious antibody or cell-mediated immune mechanism rather than a direct viral neuro-invasion, as suggested by Weyhern *et al.* (2020), although no oligoclonal bands and low interleukin-6 were found in the CSFs.

The rapid clinical improvement (i.e. 6, 2, and 7 days for Cases 1, 2 and 3, respectively) after immunotherapy was in striking contrast with the protracted persistence of neurological impairment (24, 30, and 31 days, respectively after sedation withdrawal) before treatment initiation. Such a feature supports an inflammatory or immune process. In the instance of critical illness, delayed awakening and cognitive impairment, such as delirium, may result from many factors, such as hypoxic encephalopathy, metabolic disturbances, or side effects

of sedation in the case of ICU patients (Mazeraud *et al.*, 2018). However, ICU-related brain injuries had never been reported to be responsive to immunotherapy. Although we cannot rule out a spontaneous recovery, the rapid improvement after immunotherapy initiation seems to point towards a therapeutic effect of immunotherapy.

Differences between responders and non-responders

PLEX and corticosteroid responders (Cases 1, 2 and 3) and non-responders (Cases 4 and 5) shared similar disease courses (severe COVID-19-related ARDS, mechanical ventilation and sedation for several weeks, severe consciousness impairment, which persisted several weeks after sedation withdrawal, unremarkable CSF findings).

Differences in treatment response may be related to lesion intensity observed on MRI between the two groups. The responders mainly had small deep white matter lesions while non-responders had more diffuse confluent lesions of the deep white matter. Time of treatment from diagnosis does not seem to be a relevant factor since non-responders received immunotherapy earlier compared to responders (40 and 42 days after COVID-19 symptoms onset for the non-responders, versus 48, 52 and 66 days for the responders). Another cause of treatment failure can also be related to the underlying mechanism: non-responders may have had irreversible necrotic lesions related to vasculopathy and coagulopathy as often seen after COVID-19 infection, especially in the lungs (Helms *et al.*, 2020).

Taken together, our findings support the hypothesis that immunotherapy combining PLEX and corticosteroids can be effective in the treatment of severe COVID-19-related encephalitis. The exact pathophysiological mechanism underlying brain injury has not yet been clarified but a host-immune response to SARS-CoV-2 appears to be a plausible hypothesis.

Data availability

Detailed data are available upon request to the corresponding author.

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Competing interest

The authors report no competing interests.

Supplementary material

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Table 1 Clinical presentation and time course of the disease.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Age (years) /sex	49 /M	56 /M	61 /M	37 /M	77 /F
Past medical history	Kidney transplant (rheumatoid purpura)	High blood pressure	Pulmonary sarcoidosis Heparin-induced thrombocytopenia	Obesity	Obesity High blood pressure Asthma
Clinical features at admission in ICU					
COVID-19 symptoms	Fever, cough, shortness of breath	Fever, fatigue, shortness of breath	Fever, fatigue, shortness of breath, gait disturbances, doubt about a paresis of the right hand	Dry cough, odynophagia, headache	Fever, fatigue, cough, shortness of breath, headache, anosmia
Delay between COVID-19 onset and mechanical ventilation (days)	10	6	0	10	10
Duration of mechanical ventilation (days)	59	93	83 (still ongoing on 18 June 2020)	60	65
SAPS II	38	58	65	50	41
Prone positioning sessions	Yes	Yes	No	Yes	Yes
Renal replacement therapy	Yes	Yes	Yes	Yes	No
Catecholamines[a]	Yes	Yes	Yes	Yes	Yes
Clinical features at sedation withdrawal and treatments					
Duration of sedation (days)	18	30	17	23	12
Neurological symptoms after sedation withdrawal	Unresponsive wakefulness syndrome Brainstem impairment Movement disorders	Coma Brainstem impairment	Unresponsive wakefulness syndrome Brainstem impairment Movement disorders Dysautonomia	Unresponsive wakefulness syndrome	Unresponsive wakefulness syndrome
Corticosteroid injections (No.) / PLEX sessions (No.)	10 / 5	5 / 5	5 / 10	10 / 10	5 / 5
COVID-19 symptoms onset to intravenous corticosteroids /PLEX (days)	52 / 57	66 / 69	49 / 48	42 /45	40 /50
Sedation withdrawal to intravenous corticosteroids /PLEX (days)	24 /29	30 /33	32 /31	9 /12	18 /28
First PLEX to neurological improvement (verbal commands following, days)	**6**	**2**	**7**	No improvement	No improvement

COVID-19 = coronavirus disease 2019; ICU= intensive care unit; NP = not performed; PLEX = plasma exchange; SAPS II = simplified acute physiology score 2; SARS-CoV-2 = severe acute respiratory syndrome coronavirus.

[a]Epinephrine > 0.1 μg/kg/min OR norepinephrine > 0.1 μg/kg/min

Table 2 Complementary explorations findings.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CSF testing					
Cellularity, cells/mm^3	0	1	4	10	0
Protein levels, g/l	0.32	0.26	1.54	0.18	0.18
Oligoclonal bands	Absence	Absence	Absence	Absence	Absence
IL-6 levels in CSF, pg/ml (reference value <6.5 pg/ml)	<2.5	4	8	NP	< 2.5
SARS-CoV-2 RT-PCR	Negative	Negative	Negative	Negative	Negative
Onconeural antibodies	Negative	Negative	Negative	Negative	Negative
Other complementary explorations					
IL-6 levels in serum, pg/ml (reference value <6.5pg/ml)	59.7	6	181.3	71.7	33.6
Onconeural antibodies	Negative	Negative	Negative	Negative	Negative
EEG results	Non-specific frontal and temporal slow activity	Non-specific slow-wave activity, poorly reactive, without any epileptic patterns	Non-specific slow-wave activity, reactive to auditory stimuli, without any epileptic patterns	Non-specific diffuse slow-wave activity, unreactive, without any epileptic patterns	Non-specific diffuse slow-wave activity, inconstantly reactive, without any epileptic patterns
Brain MRI results	Deep hemispherical bilateral white matter lesions on T_2/FLAIR with gadolinium enhancement on T_1. Left posterolateral lesions of the pons on T_2/FLAIR	Pontine tegmentum lesion on T_2/FLAIR Small haemorrhagic lesion of the left parietal lobe on SWAN Multiple pontine microhaemorrhages within the tegmentum on SWAN	Bilateral diffuse lesions of the deep subcortical white matter on T_2/FLAIR Multiple microhemorrhages of the corpus callosum on SWAN	Several confluent periventricular and deep supratentorial white matter lesions on T_2/FLAIR Gadolinium-enhanced symmetrical bilateral focal lesions of centrum semiovale, pallidum and periventricular white matter on T_1	Several confluent periventricular and deep supratentorial white matter lesions on FLAIR, mostly with necrotic centers and slight peripheral gadolinium enhancement on T_1
Spinal cord MRI	Normal	Normal	NP	Normal	Normal
Somatosensory evoked potential	NP	Bilateral presence of N20	Bilateral presence of N20	Bilateral presence of N20	NP
Electroneuromyography	NP	Signs of critical illness polyneuropathy	Complete abolition of sensory and motor potential in four limbs	NP	NP

COVID-19 = coronavirus disease 2019; IL-6 = interleukin-6; FLAIR = fluid-attenuated inversion recovery; SWAN = susceptibility weighted magnetic resonance sequences; NP = not performed; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.