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





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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 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 therapeutic plasma exchanges (TPE) and corticosteroids. The dramatic improvement in three 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 TPE 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 1–3) 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 2–4). 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 1–3) 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 TPE 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 1–3) 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 coronavirus-associated encephalitis ([Weyhern et al., 2020](#)), and TPE 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., 2020](#)). 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 CSF.

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 ([Fischer et al., 2020](#)), the rapid improvement observed after immunotherapy initiation in the present case series seems to point towards a therapeutic effect of immunotherapy.

Differences between responders and non-responders

TPE and corticosteroid responders (Cases 1–3) 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,

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	6	10	10
Duration of mechanical ventilation (days)	59	93	83 (still ongoing at time of writing)	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 (n) / TPE sessions (n)	10 / 5	5 / 5	5 / 10	10 / 10	5 / 5
COVID-19 symptoms onset to intravenous corticosteroids / TPE (days)	52 / 57	66 / 69	49 / 48	42 / 45	40 / 50
Sedation withdrawal to intravenous corticosteroids /TPE (days)	24 / 29	30 / 33	32 / 31	9 / 12	18 / 28
First TPE 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; SAPS II = simplified acute physiology score 2; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TPE = therapeutic plasma exchange.
^aEpinephrine > 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 < 6.5 pg/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 (see Supplementary Fig. 1)	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
Electroneurography	NP	Signs of critical illness polyneuropathy	Complete abolition of sensory and motor potential in four limbs	NP	NP

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

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 TPE and corticosteroids can be effective in the treatment of severe COVID-19-related encephalitis. The exact pathophysiological mechanism underlying brain injury has yet to be 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

Supplementary material is available at *Brain* online.

Appendix I

CoCo-Neurosciences Study Group

For full details, see the Supplementary material.

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