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ORIGINAL ARTICLE

Myoclonus in patients with COVID-19: Findings of autoantibodies against brain structures in cerebrospinal fluid

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Abstract

Background and purpose: COVID-19 is associated with multiple neurological manifestations. The clinical presentation, trajectory, and treatment response for three cases of myoclonus during COVID-19 infection, with no previous neurological disease, are decsribed.

Metods: Analysis of cerebrospinal fluid from the cases using indirect immunohistochemistry.

Results: Antibodies against rodent brain tissue, and similarities in staining patterns were observed, indicating the presence of antineuronal immunoglobulin G autoantibodies targeting astrocytes in the hippocampus.

Conclusion: Our results demontrate cerebrospinal fluid antineuronal antibodies indicating an an autoimmune involvment in the pathogenesis in COVID-19 associated myoclonus.

KEYWORDS
astrocytes, autoantibodies, COVID-19, indirect immunohistochemistry, myoclonus, treatment

INTRODUCTION

Neurological manifestations in COVID-19 are broad and may be caused by a direct effect of the virus on the nervous system or a parainfectious or postinfectious immune-mediated inflammation [1–3]. In most cases with neurological involvement in COVID-19, there is no evidence of cerebrospinal fluid (CSF) infection [4]. There are, however, frequent reports of encephalitis ensuing acute infection, including presumed autoimmune encephalitis, but cases in which autoantibodies in CSF have been screened for and identified are few [5–8]. In addition, cases with myoclonia associated with COVID-19 have been described [9–14].

Here we present the clinical course and treatment of three cases of severe COVID-19 encephalopathy with neurological symptoms including prominent myoclonus and results from indirect immunohistochemistry (IHC) on perfused mouse brain and microscopical findings.

STATEMENT OF ETHICS

Ethical approval was acquired by the Regional Ethical Review Board in Uppsala, Sweden (No. 2012/081 and 2014/148) and the National Ethical Review Authority (No. 2020–01623). Written informed

consent was obtained from the patients. All animal experiments conformed to the European Communities Council Directive (86/609/EEC) and were in accordance with Swedish laws and regulations, and approved by the local ethical committee (Stockholm Animal Ethical Committee N183/14).

MATERIAL

Patients

Data were obtained from three patients admitted to Uppsala University Hospital and other associated regional hospitals during December 2020 to January 2021.

Controls

CSF and serum taken from four female and two male volunteers were used as controls. Controls were extensively screened and are healthy, with no prior psychiatric or neurological comorbidity. Mean age was 29 years (SD=2.1).

METHODS

Indirect immunohistochemistry

See Supplementary Methods section in Data S1 for details. In brief, brains for indirect IHC were collected from 4% paraformaldehyde-perfused p56 mice and sectioned (16 μm). After background blocking steps, sections were incubated overnight with either CSF (diluted 1:4) or serum (diluted 1:1000) available from cases and controls. Whereafter, secondary horseradish peroxidase-conjugated anti-human immunoglobulin (Ig)G, IgA, and IgM were labeled separately with tyramide signal amplification fluorescent cyanine dyes.

Microscopical assessments

The immunostained sections were scanned using the Zeiss imager Z2 microscope and Metafer slide scanning system. Each Tyramide Signal Amplification (TSA) channel was visualized with a set of integration times ensuring complete coverage of intensities. Images of the reported regions were analyzed by blinded evaluators using ImageJ. Subregions were manually selected, first based on 4'6-diamidino-2-phenylindole (DAPI); then signals from suspected artifacts were removed. The mean, median, 95% confidence interval (CI), and 75% CI of intensity values were measured, and the background value for each specific TSA channel was subtracted to eliminate nonspecific binding and illumination (Figure 2). The staining patterns were then qualitatively examined microscopically by two observers (J.M. and I.L.) and determined by morphological similarities to known cell markers and cell subunits [15]. Coexistence between CSF and the astrocyte marker glial fibrillary acidic protein (GFAP) was assessed using a confocal Zeiss LSM880 microscope.

RESULTS

Case 1

A male patient in his 70s, presented to the emergency room (ER) after a 3-day history of fever, confusion, and involuntary jerks affecting his whole body, which was interpreted as generalized myoclonus. His medical history was remarkable for coronary artery grafting. At admission, respiratory symptoms were mild, with O_2 saturation 95%, and there were no signs of systemic inflammation with C-reactive protein 3.6 mg/L and D-dimer 0.9 mg/L. His condition worsened with dyspnea due to the myoclonus and impairment of consciousness, and he was subsequently intubated and sedated with propofol; the diagnosis meningitis/encephalitis was suspected. A nasal swab for COVID-19 qualitative real-time reverse-transcription polymerase chain reaction test was positive. A lumbar puncture showed pleocytosis with 11 monocytes (Table 1). Glucose, protein, and albumin levels were normal. An array for a meningitis/encephalitis panel was negative. Antibodies against NMDAR, LGI1, CASPR2, $GABA_{B1}R$, $GABA_{B2}R$, AMPA1, AMPA2, Ri, Yo, Ma2, CV2, Hu, and amphiphysin were negative using a commercial assay (Euroimmun). Magnetic resonance imaging (MRI) of the brain showed normal gray and white matter differentiation and no diffusion abnormalities. Continuous electroencephalogram (EEG) showed nonspecific slowing without epileptiform activity despite ongoing generalized myoclonus. Antiseizure medication with levetiracetam had no effect on the myoclonus, and after 6 days, intravenous immunoglobulins (IVIGs) were started. Neurological symptoms improved, and after 12 days the patient could leave the intensive care unit (ICU). After rehabilitation, he was discharged home without any remaining neurological symptoms.

Case 2

A male patient in his 50s had fever and cough for 10 days and tested positive for SARS-CoV-2. His medical history was remarkable for asthma and radically treated localized cancer. On day 11 from onset of symptoms he came to the ER with confusion and dyspnea. He suffered from acute respiratory failure with O_2 saturation 85% despite administration of 15 L/min O_2 on a mask. Blood tests revealed systemic inflammation with C-reactive protein 219 mg/L and D-dimer 2.4 mg/L. At the ER he had a generalized seizure and was intubated and sedated with propofol and transferred to the ICU. During the stay he had multifocal myoclonus predominantly involving facial, upper extremity, abdomen, and trunk muscles, distinctly increased by auditory and tactile stimuli, known as an exaggerated startle response. Myoclonus only disappeared with deep sedation. Brain MRI,

TABLE 1 Cerebrospinal fluid findings in the three patients.

Case	Age (years)	ICU (days)	LP day[a]	CSF WBC (10^6/L)	CSF NfL (ng/L)	CSF τ (ng/L)	CSF GFAP (ng/L)	CSF IL-6 (ng/L)
1	73	12	10	11[b]	550	537[b]	70	–
2	59	36	11	0	1540[b]	358	270	15
3	77	23	15	1	2000[b]	921[b]	860	4.8

Note: Reference ranges: NfL: age 40–60 years, <890 ng/L; age >60 years, <1850 ng/L; τ: age >50 years, <479 ng/L; GFAP: age 20–60 years, <750 ng/L, age >60 years, <1250 ng/L; WBC: <5 10^6/L.

Abbreviations: CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; ICU, intensive care unit; IL-6, interleukin-6; LP, lumbar puncture; Nfl, Neurofilament light protein; WBC, White blood cells.

[a]Days from symptom onset to lumbar puncture.

[b]Value above reference range.

repeated EEG, and extensive laboratory workup including CSF were normal (Table 1). Treatment with levetiracetam and valproic acid had no effect, whereas benzodiazepines gave some improvement. He received methylprednisolone pulses for 3 days, and the myoclonus gradually improved. After 36 days, the patient was discharged from the ICU, still having some action myoclonus that completely resolved over time.

Case 3

A man in his 70s with hypertonia and diabetes mellitus fell ill with fever and confusion, and on day 3 he tested positive for SARS-CoV-2. At admission, he was slightly hypoxic (O_2 saturation 94% with 5 L/min O_2), disoriented, and had positive and negative myoclonus in the upper extremities. C-reactive protein was 94 mg/L, and D-dimer was 4.9 mg/L. On day 7 from onset of symptoms, his condition deteriorated with declining consciousness and increasing breathing difficulties, and he was intubated. He was sedated and treated with steroids, levetiracetam, and benzodiazepine. On wake-up testing, multifocal myoclonus was noticed in the eyelid and facial and upper extremities muscles. Extensive blood and CSF workup were unremarkable except for findings of anti-Yo and Recoverin antibodies in serum (Table 1). Repeated EEG showed cerebral slowing without epileptiform activity. Brain MRI was normal except for an old infratentorial infarct and a few parietal microbleeds of unknown date. A whole body FDG-PET scan was performed in the subacute stage to rule out malignancy. The brain images were normal without signs of neuroinflammation by means of altered glucose metabolism [16]. The patient was treated with plasmapheresis and after 3 weeks could be weaned off from the respirator and eventually transferred to a post–COVID-19 rehabilitation ward. Clinically, he no longer had myoclonus but pronounced neurological sequels with cognitive dysfunction and parkinsonistic features.

Indirect immunohistochemistry

Indirect IHC was performed on CSF and serum taken in connection with the initial illness and before any immune modulation treatment was given. IHC displayed similar staining patterns in both CSF and serum for all cases. The most distinct staining pattern indicated autoantibodies targeting astrocyte-like structures in the hippocampus. This pattern was not found in any of the controls, who either displayed a nonspecific staining pattern or no staining (Figure 1). The three different Ig subclasses IgG, IgA, and IgM were investigated separately, and the astrocyte-like structures pattern was only seen for IgG. IgM levels did not differ from controls. Elevated ant-brain IgG and IgA autoantibodies were seen in multiple brain regions with staining intensities >2 SDs from healthy controls (Figure 2). CSF staining patterns for IgA, although greater in intensity, did not show specific reactivity against astrocytes or other structures.

Costaining with GFAP, a marker for astrocytes, showed only partial overlap with patient CSF-derived IgG antibodies, indicating binding of CSF to unknown target in astrocytes (see Figure 3).

DISCUSSION

Para- and postinfectious myoclonus in relation to COVID-19 has previously been described [13, 17]. We present three cases with COVID-19 encephalopathy with prominent myoclonus with an onset in relation to severe COVID-19 infection. None of the patients had a history of seizures. By using indirect immunofluorescence on perfused mouse brain tissue, CSF-derived IgG immunoreactivity was measured in several mouse brain regions, indicative of an autoimmune mechanism causing the symptoms.

Myoclonus in critically ill patients can result from a range of etiologies [18]. In our cases, medication toxicity, cerebral hypoxia, metabolic derangements, and cerebral infection were ruled out. Metabolic activity was normal as observed by measuring liver enzymes, creatinine, blood urea nitrogen, estimated glomerular filtration rate, electrolytes, and calcium. Because no epileptiform activity was seen on EEG, the myoclonus was interpreted as originating from subcortical or brain stem structures. Unfortunately, a more detailed analysis of the myoclonia with electromyography was never performed. Only one patient was investigated with Fluorodeoxyyglucose-positron emission tomography (FDG-PET) FDGPET without any significant findings such as altered metabolism, which has been reported in connection with subacute COVID-19

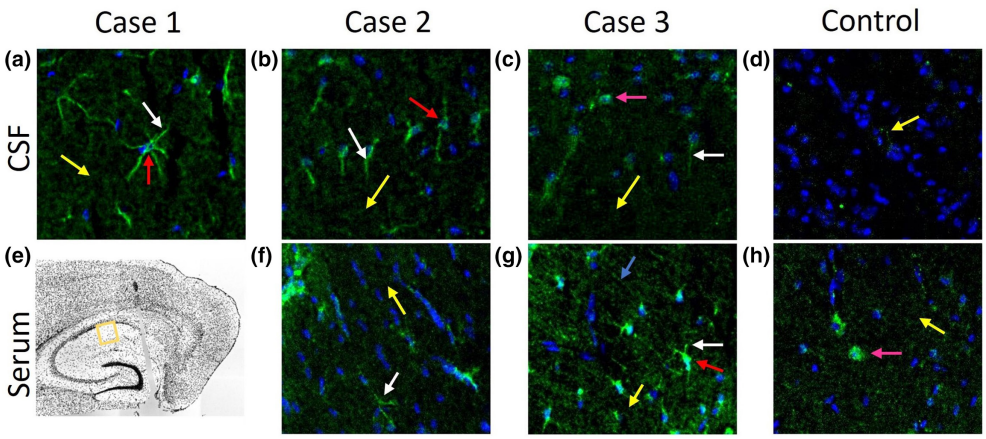

FIGURE 1 Indirect immunohistochemistry (IHC) shows immunoglobulin (Ig)G reactivity against brain structures in mouse tissue in both serum and cerebrospinal fluid (CSF). IHC staining using both CSF and serum displayed astrocytic-like staining in all cases compared to healthy controls, using anti-IgG as a secondary antibody (green) and counterstaining using 4'6-diamidino-2-phenylindole (DAPI) (blue). (a) CSF from Case 1 shows astrocytic-like staining of the cell body and processors in the stratum radiatum in the CA1 region of the hippocampus. (b) CSF from Case 2 shows astrocytic-like staining of the cell body and processors in the stratum radiatum in the CA1 region of the hippocampus. (c) CSF from Case 3 shows astrocytic-like processors staining in the white matter between the subiculum and cortex as well as a cytosolic neuronal-like staining in the subiculum. Weak staining in the stratum radiatum in the CA1 region of hippocampus was also observed. (d) No astrocyte-like staining was measured in healthy controls. The yellow arrow shows very weak neuropil staining seen in some controls (arrow). (e) Presentation of the region selected in the images. Serum for Case 1 was not available. (f) Serum from Case 2 shows astrocytic-like processors in the white matter. (g) Serum from Case 3 shows both dendritic neuronal staining from the granular layer into the stratum radiatum in CA1 region of the hippocampus as well as an astrocyte-like cell body and processors in the stratum radiatum layer of CA1 region in the hippocampus. (h) Image demonstrates higher background in serum from healthy controls with antineuronal antibodies as well as neuropil staining; however, no astrocyte-like staining was detected in serum in the controls. White arrows indicate astrocyte-like processors, red arrows astrocyte-like cell body, purple arrows neuronal-like cell body, orange arrows neuronal dendrite, and yellow arrows neuropil.

and cognitive impairment [16]. Treatment with levetiracetam, valproic, and benzodiazepines had insufficient effect. Assuming the symptoms were caused by an immune mechanism, the patients received immunomodulatory treatment. Two patients received methylprednisolone and IVIG with partial response. A distinct response was noted in one patient who received plasmapheresis.

In patients with neurological symptoms associated with severe COVID-19, autoantibodies of neuronal targets have been identified [18] in serum and sometimes in CSF. In one of the patients, an antibody panel was positive for Recoverin and anti-Yo in serum. A malignancy workup did not reveal any random malignancy, suggesting an unspecific autoreactivity of the immune system in relation to SARS-CoV-2 infection [19].

Two patients recovered eventually without any neurological sequelae. One patient had persistent lingering symptoms with cognitive and motor impairment. Notably, this patient had an increased level of a biomarker for axonal damage Neurofilament light (Nfl), which is known to be associated with disease severity in COVID-19 neurological manifestations [20] and other forms of autoimmune encephalitis [21, 22].

Previously studied COVID-19–positive patients have displayed a strong IgG autoreactivity in mouse brain tissue and similar patterns of antiastrocytic as well as neuropil staining [17]. The astrocytic staining pattern was only observed further in the patients with myoclonus. They also shared the staining pattern similarity of another case with limited astrocytic-like staining that responded to steroid treatment [23]. In a screening for antineuronal autoantibodies in CSF using a similar method, only one case with astrocytic staining pattern was described among the 121 patients with severe psychiatric states [24]. The frequency of this specific pattern in other postinfectious contexts is not yet known.

All three cases shared CSF immunohistochemical reactivity similarities that in blinded evaluation differentiated them from controls. Double staining with GFAP localized the staining to a subset of astrocytes, but the minimal overlap suggests a different antigen target. A similar astrocyte-like staining pattern was also found after retrospective analysis of a case of malignant catatonia after COVID-19; however, this case showed additional immunoreactivity not seen in the present cases [5]. The staining patterns did not resemble cases with antibodies against Anti-*N*-methyle-*D*-aspartate (NMDA) receptors or the pattern seen for our other cases with neurological manifestations (acute necrotizing encephalopathy, acute disseminated encephalomyelitis) associated with COVID-19 [6]. These findings are in line with the growing numbers of targets for brain autoantibodies [25].

A finding of potential interest was the relatively rapid symptom onset in relation with COVID-19 debut and the lack of IgM reactivity, whereas other cases with acute onset of symptoms several weeks after infection showed IgM reactivity in our method (data not shown). These findings suggest that the B-cell clones producing the

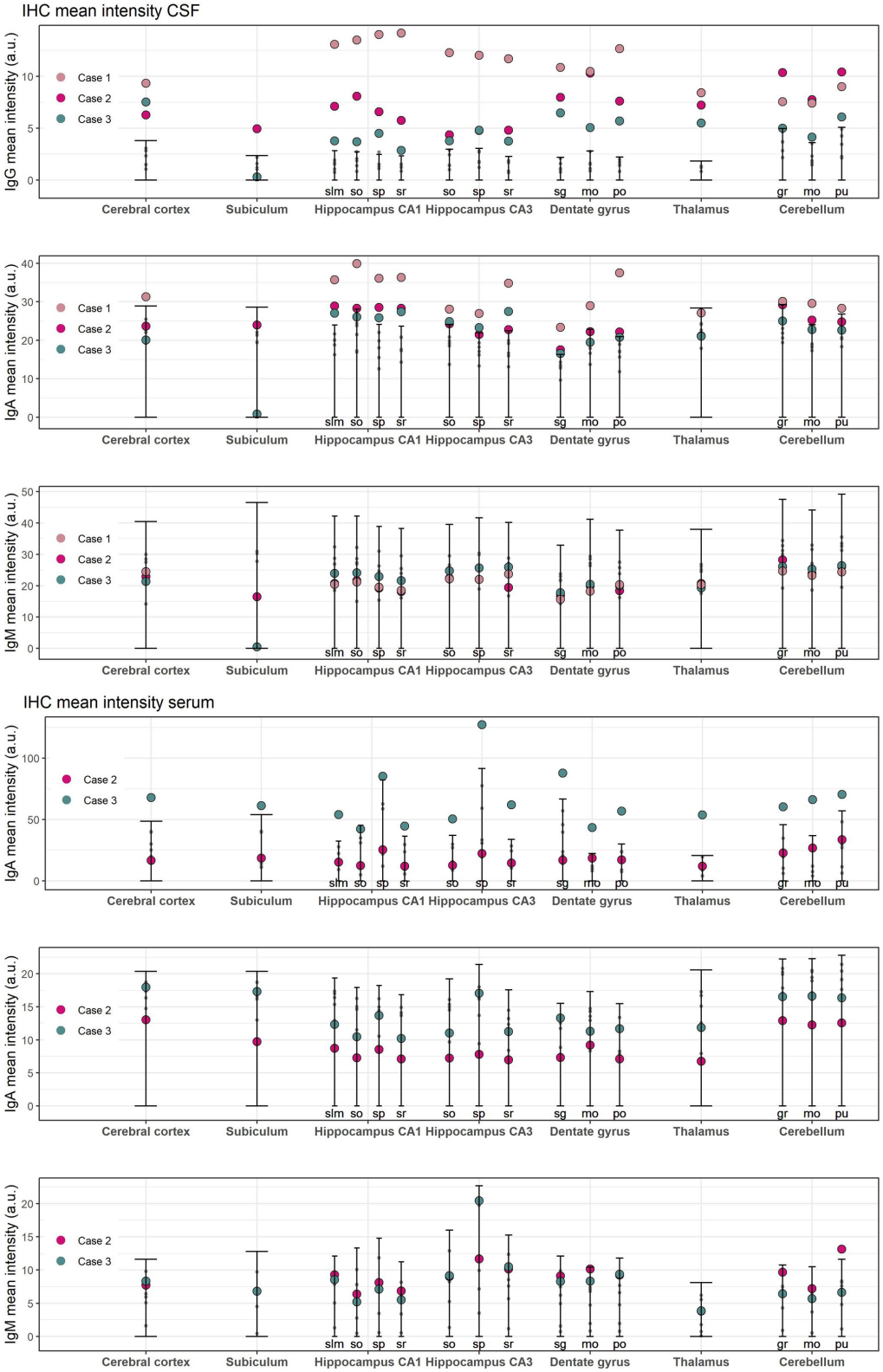

FIGURE 2 Indirect immunohistochemistry (IHC) shows elevated general staining intensity for anti-brain antibodies in patients compared to controls particularly in cerebrospinal fluid (CSF). Multiplex analysis of antibody subtypes immunoglobulin (Ig)G, IgM, and IgA was performed together with counterstaining with 4'6-diamidino-2-phenylindole (DAPI). Digital analysis was based on a control cohort without a comorbidity as references for normal variation ($n = 6$). Shown are the mean signal intensities in seven brain regions corrected for background. Healthy controls are shown in black, and error bars are based on the mean intensities ±2 SDs from the controls. Staining intensities are strongest for Cases 1 and 2 in all investigated brain regions; however, intensity values above 2 SDs from controls are displayed for all cases in CSF for IgG and IgA but not IgM. Serum was available for Case 2 and 3 and staining intensity >2 SDs compared to controls was only seen for Case 3 in IgG. mo, molecular layer; gr, granular layer; po, polymorph layer; pu, purkinje layer; sg, granule cell layer; slm, lacunosum layer; so, oriens layer; sp, pyramidal layer; sr, radiatum layer.

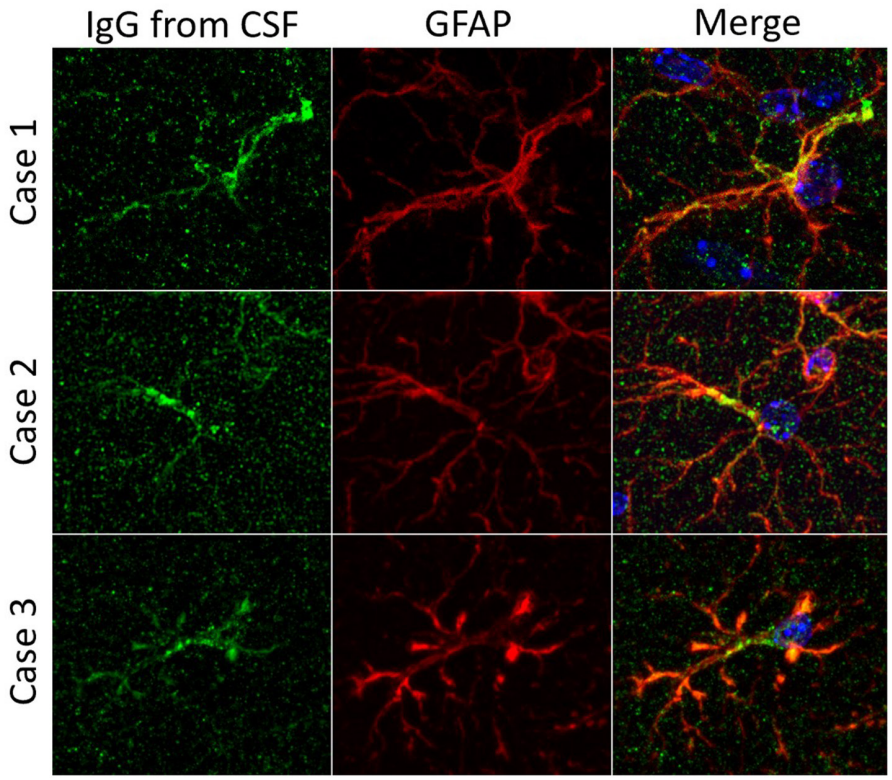

FIGURE 3 Indirect immunohistochemistry demonstrates cerebrospinal fluid (CSF)-derived anti-neuronal immunoglobulin (Ig)Gs that are reactive against an unknown target in hippocampal cells that express the astrocytic cell marker glial fibrillary acidic protein (GFAP). Sagittal mouse brain sections were stained with CSF IgG from cases 1–3 (green, column IgG from CSF) and the astrocytic cell marker GFAP (red, column GFAP). Column merge show merged images counterstained using 4'6-diamidino-2-phenylindole (DAPI) arbitrary units (a.u.) (blue) displaying a coexistence but not complete overlap between IgG and GFAP.

anti-brain antibodies were derived from preexisting memory cells in these cases. There are emerging data that suggest that COVID-19 is associated with a bystander polyclonal autoreactive B-cell activation and elevated levels of pathogenic autoreactive IgGs [26, 27]. Improved recognition of autoantibody contributions to peri- and postinfection phenotypes may open new treatment modalities targeting B cells [28].

Limitations

This study had limitations associated with a descriptive retrospective case series. The healthy individuals who donated CSF were not matched for age, sex, or comorbidities. Unfortunately, there were no samples from patients with other severe systemic infections for comparison, and therefore we could not determine how specific the brain antibodies are for COVID-19 infections. In addition, there was no follow-up of the patients to evaluate a possible normalization of the immunological autoreactivity. This study may, however, generate hypotheses and raise interest in further and larger studies of similar entities.

CONCLUSIONS

Our results demonstrated CSF antineuronal antibodies, which indicates autoimmune involvement in the pathogenesis of COVID-19–associated myoclonus that responded to immunotherapy. The findings illustrate the potential value of tissue tests in adding weight to clinical assessments and decision to treat in cases where indications for neuroinflammation are subtle. A future study of more patients with COVID-19 as well as other systemic severe infections is warranted.

AUTHOR CONTRIBUTIONS

Isa Lindqvist: Methodology, formal analysis, data curation, visualization, writing–original draft, writing–review & editing. **Janet L. Cunningham**: Writing–review & editing, conceptualization, methodology, formal analysis, writing–original draft, funding acquisition; supervision. **Jan Mulder**: Formal analysis, methodology, supervision, writing–review & editing. **Amalia Feresiadou**: Investigation, writing–review & editing. **Elham Rostami**: Investigation, writing–review & editing, funding acquisition. **Johan Virhammar**: Conceptualization, investigation, visualization, writing–review & editing, data curation. **Eva Kumlien**: Conceptualization, data curation, writing–original draft, investigation, writing–review & editing, funding acquisition. All authors reviewed the results and approved the final version of the article.

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CONFLICT OF INTEREST STATEMENT

J.L.C. has received lecturing fees from Otsuka Pharma Scandinavia, Janssen-Cilag AB, and H. Lundbeck AB.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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