LETTER TO THE EDITORS

Intravenous immunoglobulins for treatment of severe COVID-19-related acute encephalopathy

Shufan Huo1,2,3 · Caroline Ferse4 · Fabian Bösl1 · S. Momsen Reincke1,5 · Philipp Enghard4 · Carl Hinrichs4 · Sascha Treskatsch6 · Stefan Angermair6 · Kai-Uwe Eckardt4 · Heinrich J. Audebert1,2 · Christoph J. Ploner1,7 · Matthias Endres1,2,3,5,7 · Harald Prüss1,5 · Christiana Franke1 · Franziska Scheibe1,8

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Dear Sirs,

Coronavirus disease 2019 (COVID-19) patients on intensive care units (ICU) frequently present with acute encephalopathy that appears to be distinct from other ICU-related encephalopathies regarding higher incidence, longer duration, and increased severity including autonomous dysregulation and non-satisfactory response to neuroleptic drugs [1]. According to the updated nomenclature of delirium and acute encephalopathy, we use the term acute encephalopathy to describe a rapidly developing pathobiological brain process, expressed clinically as delirium, sub syndromal delirium or coma with partly additional neurological findings such as extrapyramidal signs or seizures [2]. This type of acute encephalopathy is associated with delayed recovery, weaning failure, prolonged ICU or hospital stay, or even impaired clinical outcome.

First reports found positive responses of COVID-19-associated encephalopathy to immunotherapy [3–5] that supported the hypothesis of a possible inflammatory pathomechanism [6]. However, this encephalopathy might still be misjudged by intensivists as poorly treatable with limited prognosis, risking premature withdrawal of ICU therapy or even end-of-life decisions in affected patients. Therefore, our case series demonstrates a promising and rapid effect of intravenous immunoglobulins (IVIg) on otherwise treatment-refractory acute encephalopathy in COVID-19 patients on ICU.

This retrospective, single-center case series included 12 patients with critical courses of COVID-19 requiring treatment at ICU, who developed a severe encephalopathy (leading to clinical presentation of hyper- and/or hypoactive delirium [2]) of at least 1 week without satisfactory response to neuroleptic drugs and/or even sedatives. These patients were treated with 2 g/kg IVIg over 3–5 days as off-label, individual medical treatment. The dosage of IVIg was chosen pragmatically according to established therapeutic regimens in other neurological autoimmune-mediated diseases.

Other causes of encephalopathy such as increased blood levels of sedative medication, intoxication, metabolic changes (abnormal electrolyte concentrations, hyperuricemia, hepatic encephalopathy, hypo- or hyperglycemia),

Shufan Huo and Caroline Ferse have contributed equally.

Christiana Franke and Franziska Scheibe have contributed equally.

Shufan Huo
shufan.huo@charite.de

1 Department of Neurology and Experimental Neurology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Charitéplatz 1, 10117 Berlin, Germany
2 Center for Stroke Research Berlin, Charité-Universitätsmedizin Berlin, Berlin, Germany
3 DZHK (German Centre for Cardiovascular Research), partner site Berlin, Berlin, Germany
4 Department of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
5 German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany
6 Department of Anesthesiology and Intensive Care Medicine, Charité-Universitätsmedizin Berlin, Freie Universität and Humboldt-Universität zu Berlin, Berlin, Germany
7 Berlin Institute of Health at Charité-Universitätsmedizin Berlin, Berlin, Germany
8 NeuroCure Cluster of Excellence, Charité-Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany
sepsis with fever, hypothermia, shock or hypoxia were excluded. All patients received treatment with 6 mg dexa-methasone for at least 10 days according to the RECOVERY study protocol [7].

After occurrence of acute encephalopathy and prior to IVlg therapy, all patients received imaging with either cerebral CT or MRI and one-time cerebrospinal fluid (CSF) examinations (except patient #8, whose critical clinical status did not permit lumbar puncture) with measurement of standard laboratory parameters. Antineuronal autoantibodies (namely: IgG-antibodies against amphiphysin, PNMA2 (Ma2/Ta), Ri, Yo, Hu, CV2 (CRMP5), Tr (DNER), NMDA receptor, GABA-b receptor, AMPA receptor1/2 (GlulA1/GluA2), mGlur5, Glycin receptor, Dopamin2 receptor, DPPX, LGII, CASPR2, Aquaporin-4, Myelin, GAD65) were determined by cell-based indirect immunofluorescence assays at Labor Berlin or Euroimmun, Germany. A PCR-screening for common neurotropic pathogens (namely: SARS-CoV-2, herpes simplex virus 1/2, varicella zoster virus, human herpes virus 6, Epstein–Barr virus, cytomegalo-virus, enterovirus, parechovirus, Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Listeria monocytogenes, group B streptococcus, Escherichia coli (K1), and cryptococcus) excluded other common CNS infections. Additionally, indirect immunofluorescence technique on unfixed murine brain sections was applied with CSF and serum according to previously published protocols [8]. The inflammatory marker IL-6 was measured routinely every other day with Elecsys® IL-6 immunoassay (Roche) and Immulite IL-6 (Siemens). Neurofilament light chain was determined in serum with Simoa NF-light™ assay (Quanterix) and in CSF with NF-light™ ELISA (UmanDiagnostics).

Clinical neurological outcome was continuously evaluated by a neurologist and reported immediately before initiation and after termination of IVlg therapy and at discharge. Outcomes were assessed by Confusion Assessment Method for ICU (CAM-ICU), Richmond Agitation–Sedation Scale (RASS), Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS) and modified Rankin Scale (mRS). Standardized scores were primarily ascertained by the treating neurologist. In case of missing data, scores were obtained from the daily routine assessment by the ICU nurses.

The patient cohort (n = 12) had a median age of 67 years (range 43–77, two females), required a median of 61 days (range 33–160) of ICU treatment and presented high rates of multi-organ failure with invasive ventilation in 11 (92%, n = 9 prone positioning, n = 2 veno-venous extracorporeal membrane oxygenation), pulmonary superinfections in 11 (92%), hepatic failure in five (42%), renal replacement therapy in nine (75%) and catecholamine therapy in all patients (Table 1). After a median of 23 days (range 0–37) after hospital admission due to COVID-19, all patients developed encephalopathy, requiring continuous intravenous sedation in 10 patients (83%, Table 2).

Cerebral CT or MRI showed none or only unspecific findings, but no abnormalities explaining the observed encephalopathy (Table 3). CSF was taken in 11 patients. In accordance with a recently published study about CSF findings in COVID-19 [9], eight of our patients showed blood brain barrier (BBB) dysfunction and all yielded normal cell counts and negative PCR for common pathogens including SARS-CoV-2. Furthermore, nine patients displayed either low-titer antineuronal antibodies in serum (Myelin, CASPR2, NMDAR, Yo), or IgG binding of unknown specificity in indirect immunofluorescence of blood and CSF on unfixed murine brain sections, or both (Table 3). Increased neurofilament light-chain values in serum and CSF of all investigated patients (measured in n = 11 of 12) reflected relevant neuronal degeneration or damage.

All patients received IVlg treatment at a median of 25 days (range 10–37) after acute encephalopathy onset and a median of 48 days (range 32–54) after hospital admission as ultima ratio therapy. Nine of 12 patients (#1–9, 75%, responders) presented milder symptoms at a median of 4 days (range 1–6) after IVlg initiation (Table 2). Three of 12 patients did not improve (#10–12, 25%, non-responders) and died of sepsis. 67% of responders had a negative CAM-ICU at discharge, while RASS improved from − 3 before therapy to 0 at discharge. Median GCS improved from 6 (range 3–12) to 14.5 (range 11–15), median GOS from 2 (range 2–3) to 3 (range 3–4) and median mRS from 5 (range 4–5) to 4 (range 3–5, Table 4). Before IVlg therapy, all patients required sedative (benzodiazepines, dexmedetomidine, clonidine, phenobarbital, propofol, esketamine, opiates) and/or neuroleptic or other CNS medication (risperidone, quetiapine, citalopram, amantadine) due to continuous encephalopathy, ongoing ventilation and ICU treatment. After IVlg administration, sedative or neuroleptic medication was successfully reduced in seven of 12 cases (Table 2). Patient #6 improved initially but died later due to sepsis. No adverse events attributable to IVlg therapy were observed.

Mean values of NfL in serum (responders 392 pg/ml, range 31–914 pg/ml, non-responders 2751 pg/ml, range 1348–4153 pg/ml) and CSF (responders 2406 pg/ml, range 981–6359 pg/ml, non-responders 14271 pg/ml, range 2215–28099 pg/ml) were higher in non-responders than in responders (Table 3). Similarly, mean values of IL-6 before IVlg treatment were lower in responders (98 ng/l, range 19–252 ng/l) compared to non-responders (438 ng/l, range 106–1087 ng/l) and decreased over the course of the treatment in responders (at discharge: 39 ng/l, range 7–99 ng/l) while increasing in non-responders (before death: 2983 ng/l, range 61–5905 ng/l, Table 3).

This case series demonstrates a therapeutic effect of IVlg in treatment-refractory COVID-19-associated acute
Table 1  Clinical presentation and duration of the disease

| #  | Age (y) | Sex | Clinical features          | Past medical history | Pulmonary superinfection | Invasive ventilation | Prone positioning | vvECMO  | Hepatic failure | RRT | Sepsis | Catecholamine therapy | Hospital stay (d) | ICU stay (d) |
|----|---------|-----|-----------------------------|----------------------|--------------------------|----------------------|-------------------|---------|----------------|-----|--------|---------------------|-----------------|-------------|
| 1  | 77      | m   | Hyperactive delirium        |                      | +                        | +                    | –                 | –       | +              | +   | +      | +                   | 81              | 81          |
| 2  | 75      | m   | Hyperactive delirium, seizures |                      | –                        | –                    | –                 | –       | +              | +   | –      | +                   | 38              | 37          |
| 3  | 62      | m   | Hypoactive delirium         |                      | +                        | +                    | –                 | –       | +              | –   | +      | +                   | 76              | 73          |
| 4  | 73      | m   | Hypoactive delirium         |                      | +                        | +                    | –                 | –       | +              | +   | +      | +                   | 58              | 57          |
| 5  | 75      | m   | Hypoactive delirium         |                      | +                        | +                    | –                 | –       | +              | +   | +      | +                   | 54              | 50          |
| 6  | 74      | m   | Hyperactive delirium, seizures, myoclonia | aHT, AF, renal transplant, obesity | +                        | –                    | –                 | +       | +              | +   | +      | +                   | 195             | 64          |
| 7  | 52      | f   | Hypoactive delirium         |                      | +                        | +                    | –                 | –       | +              | –   | +      | +                   | 55              | 55          |
| 8  | 43      | m   | Hyperactive delirium        |                      | +                        | +                    | –                 | –       | +              | +   | +      | +                   | 103             | 100         |
| 9  | 49      | m   | Hyperactive delirium        |                      | +                        | +                    | +                 | +       | +              | +   | +      | +                   | 102             | 99          |
| 10 | 59      | f   | Hypoactive delirium, myoclonia |                      | +                        | +                    | +                 | –       | +              | +   | +      | +                   | Known           | 160         |
| 11 | 55      | m   | Hypoactive delirium         |                      | +                        | +                    | +                 | –       | +              | +   | +      | +                   | 57              | 53          |
| 12 | 72      | m   | Hypoactive delirium         |                      | +                        | +                    | –                 | –       | +              | +   | +      | +                   | Unknown         | 33          |

Clinical features (pulmonary superinfection, invasive ventilation, proning, vvECMO, hepatic failure, RRT, sepsis, catecholamine therapy) are listed as “+” if they occurred at any time during the ICU stay. The term “delirium” is used in this manuscript to describe the clinical presentation of acute encephalopathy[2]. Before IVIg treatment, other sources of encephalopathy such as sepsis or hepatic failure were excluded at the time of clinical presentation of delirium, see exclusion criteria. For patients #10 and #12, the total duration of hospital stay could not be determined due to missing information about previous treatments in other hospitals. While 11 patients had at least one known cardiovascular risk factor, patient #4, who presented with known myasthenia gravis, did not. Patient #9 additionally suffered from stage II pulmonary sarcoidosis. Overall, most patients were severely affected by multiple complications (e.g., sepsis in 11, need for invasive ventilation in 11, renal failure with need of replacement therapy in nine, vvECMO in two patients)

– no, + yes, AF atrial fibrillation, aHT arterial hypertension, BMI body mass index, CAD coronary artery disease, d days, DM2 diabetes mellitus type 2, f female, ICU intensive care unit, m male, MI myocardial infarction, RRT renal replacement therapy, vvECMO veno-venous extracorporeal membrane oxygenation, y years
### Table 2 Detailed clinical and time course: changes of CNS medication

| #   | Clinical status                                                                 | CNS medication                                | Time delirium onset after admission (d) | Time delirium onset—IVIg start (d) | Time IVIg start—improvement (d) |
|-----|---------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------|-------------------------------------|----------------------------------|
| 1   | Agitation, myoclonia, no GF                                                     | Adequate communication, intermittent agitation| 15                                     | 37                                  | 1                                |
| 2   | Agitation, no GF, no communication                                             | Morphone, Risperidone                         | →                                      | →                                   | 0                               |
| 3   | Drowsiness, no GF, vegetative stress upon weaning                              | Adequate communication, RTC, agitation, panic| 36                                     | 12                                  | 3                                |
| 4   | Intermittent GF, no communication, tetraplegia                                 | No delirium                                   | →                                      | none                                | 24                              |
| 5   | Coma, tetraplegia                                                              | Amantadine, Morphone                          | →                                      | N/A                                 | 14                              |
| 6   | Somnolent, GF, disoriented, no RTC, dysarthria, myoclonia                       | Risperidone                                   | →                                      | none                                | 22                              |
| 7   | No GF, no response to stimulus                                                 | Clonidine, Sufentanil                         | none                                  | Melperon                            | 10                              |
| 8   | Severe agitation, skew deviation                                                | Dexmedetomidine, Esketamine, Morphone, Phenobarbital, Propofol | ↓                                      | nd                                  | 6                               |
| 9   | Agitation, no GF, myoclonia, brachiofacial dyskinesia                          | Diazepam, Morphone, Risperidone               | ↓                                      | nd                                  | 4                               |
| 10  | GF, RTC, visual hallucinations                                                  | Citalopram, Clonidine, Sufentanil             | ↑                                      | N/A                                 | 30                              |
| 11  | No response to stimulus, tetraplegia                                           | Dexmedetomidine, Lorazepam, Quetiapin, Sufentanil | ↑                                      | N/A                                 | 23                              |
| 12  | Coma, eye deviation                                                            | Sufentanil                                    | →                                      | N/A                                 | 37                              |

**This table shows the detailed clinical course upon neurological examination as well as changes in application of CNS medication. N/A is stated if the patient died before discharge. Patients #2 and #6 were discharged immediately after IVIg treatment due to clinical improvement, which is why their clinical statuses at t2 and t3 remained unchanged. For patients #8 and #9 the exact time of acute encephalopathy diagnosis could not be determined due to continuous need for sedation.**

**Clinical presentation of myoclonia:** Patient #1 and #9: generalized, patient #6: fine myoclonia of the legs

↑ increased, ↓ decreased, → no change, d days, GF gaze fixation, RTC response to commands, t1 last value before IVIg therapy, t2 first value after IVIg therapy, t3 last value before discharge or death
| #  | CT/MRI                                                                 | EEG                                      | CSF cells/µl | Oligoclonal bands CSF/serum | Reibergram          | CSF glucose mg/dl | CSF lactate mg/dl | CSF total protein mg/l | Qalb | IgG % | IgA % | IgM % |
|----|------------------------------------------------------------------------|------------------------------------------|--------------|-----------------------------|---------------------|-------------------|-------------------|----------------------|------|-------|-------|-------|
| 1  | MRI: thickened meninges, white matter lesions                          | Alpha, intermittent theta rhythm         | 2            | Type 4                      | Normal              | 85                | 16.7              | 294.6                | 6.9  | 0     | 0     | 0     |
| 2  | CT: chronic lacunar infarctions, massive leukoaraiosis                 | Alpha, intermittent theta rhythm         | 2            | Type 1                      | Barrier dysfunction | 55                | 16.7              | 792.1                | 14.4 | 0     | 0     | 0     |
| 3  | CT: mild leukoaraiosis                                                 | Theta, intermittent delta rhythm         | 1            | Type 4                      | Normal              | 127               | 17.3              | 217.8                | 4.8  | 0     | 0     | 0     |
| 4  | MRI: small SAH, several microbleeds, small chronic infarction          | Mixed theta-delta rhythm                 | 7            | Type 1                      | Barrier dysfunction | 82                | 13.2              | 717.4                | 13.8 | 0     | 13    | 45    |
| 5  | MRI: two small acute infarctions                                      | Theta, intermittent delta rhythm         | 1            | Type 4                      | Borderline barrier dysfunction | 136               | 25.1              | 354.6                | 9.3  | 0     | 0     | 0     |
| 6  | CT: leukoaraiosis                                                      | Theta, intermittent delta rhythm         | 2            | Type 3                      | Barrier dysfunction | 127               | 17.8              | 678.9                | 11.7 | 0     | 0     | 0     |
| 7  | CT: mild leukoaraiosis                                                 | Mixed theta-delta rhythm                 | 0            | Type 4                      | Barrier dysfunction | 59                | 16.8              | 379                  | 8.4  | 0     | 0     | 0     |
| 8  | CT: normal                                                            | nd                                       | nd           | nd                           | nd                  | nd                | nd                | nd                   | nd   | nd    | nd    | nd    |
| 9  | CT: partially empty sella                                              | nd                                       | nd           | nd                           | nd                  | nd                | nd                | nd                   | nd   | nd    | nd    | nd    |
| 10 | MRI: normal PET-CT: limbic encephalitis                                | nd                                       | nd           | Type 1                      | Barrier dysfunction | 97                | 17                | 864                  | 21.5 | 0     | 0     | 0     |
| 11 | CT: leukoaraiosis                                                      | nd                                       | nd           | Type 4                      | normal              | 70                | 17                | 239                  | 7.7  | 0     | 0     | 0     |
| 12 | MRI: multiple chronic small infarctions, global atrophy, leukoaraiosis | Mixed theta–delta rhythm                | 1            | Type 4                      | Borderline barrier dysfunction | 101               | 16.1              | 556                  | 25.8 | 0     | nd    | 0     |
All findings were measured after occurrence of acute encephalopathy and prior to IVIg administration except IL-6 levels, which were determined every second day throughout the ICU stay. Cerebral imaging only showed nonspecific pathologies including small ischemic strokes or intracerebral bleedings with no clinical correlation. Such imaging alterations are frequently seen in COVID-19 patients due to their higher risk of cerebral vasculopathy, especially in patients treated with vvECMO-therapy. But also activation of the coagulation system in COVID-19 patients predisposes them to thrombotic events of the brain and other organs. Patient #4 had a blood contamination in lumbar puncture with an increased CSF cell count of 7/µl and 1000 erythrocytes/µl. In all other patients CSF cell count and cytology were normal (< 5/µl, lymphocytes). Part of the CSF samples of patient #10 coagulated due to blood contamination, which is why some laboratory information is missing.

Oligoclonal bands are reported as follows: type 1: Normal CSF, type 2: Oligoclonal IgG restricted to CSF, type 3: Oligoclonal IgG in CSF with additional identical bands in CSF and serum (combination of types 2 and 4), type 4: Identical oligoclonal bands in CSF and serum.

Antineuronal antibodies in serum and CSF were tested according to a standard panel including IgG-antibodies against amphiphysin, PNMA2 (Ma2/Ta), Ri, Yo, Hu, CV2 (CRMP5), Tr (DNER), NMDAR, GABA-b-R, AMPA-R1/2 (GluA1/GluA2), mGluR5, Glycin-R, Dopamin2-R, DPPX, LGI1, CASPR2, Aquaporin-4, Myelin, GAD65. The upper limit for normal serum NfL levels is 9.9 pg/ml. The values for CSF NfL are age dependent, but values > 289 pg/ml are indicative of axonal damage of unknown specificity, whereas NfL values > 2.200 pg/ml can be found in patients with amyotrophic lateral sclerosis. NfL ratio is calculated by dividing CSF NfL by serum NfL. The increased NfL values in serum and CSF of all investigated patients reflect relevant axonal damage in affected individuals.

\[ P \text{ values show the comparison between responders and non-responders with a } t\text{-test and a standard } \alpha=0.05. \text{ Due to the limited sample size (nine vs. three subjects), these should only be interpreted on an exploratory level. Responders: patients #1–9, non-responders: patients #10–12.} \]

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\[ \uparrow \text{ increased, } Ab \text{ antibodies, CASPR2 contactin-associated protein 2, CSF cerebrospinal fluid, } CT \text{ computed tomography, EEG electroencephalography, IgA\% intrathecal fraction IgA, IgG\% intrathecal fraction IgG, IgM\% intrathecal fraction IgM, IIFT indirect immunofluorescence technique, IL-6 interleukin-6, MRI magnetic resonance imaging, nd not determined, NfL neurofilament light chain, NMDAR N-methyl-D-aspartate receptor, PET–CT Positron emission tomography–computed tomography, SAH subarachnoid hemorrhage} \]
encephalopathy. The pathophysiology of this entity remains speculative, but IVIg response points towards an immune-mediated mechanism, possibly succeeding COVID-19-induced cytokine release syndrome with BBB dysfunction and macrophage immigration or microglia activation, well in line with a neuroinflammatory hypothesis of COVID-19-associated acute encephalopathy [10]. The high frequency of intrathecal antineuronal antibodies detected by indirect immunofluorescence is in line with previous publications [8, 11] and might be a surrogate marker for autoimmune-mediated mechanisms, but whether they reflect specific or unspecific binding against CNS target epitopes causing acute encephalopathy currently remains open; especially since similar findings can be detected in asymptomatic persons. Immune-regulatory effects of IVIg are pleiotropic and involve Fc-receptor binding on macrophages and microglia, inflammation suppression including cytokines and chemokines, and transformation of activated microglia into a protective phenotype leading to reduction of neuronal cell death [12].

To date, one report described positive effects of IVIg on COVID-19-associated acute encephalopathy in five patients, but the therapeutic regimen overlapped with Tocilizumab and standardized methodology was lacking [13].

In our well-characterized cohort using standardized scores documenting responders and non-responders, natural remission coinciding the suspected IVIg effects cannot be excluded, but the long preceding interval without progress and the rapid improvement after IVIg initiation suggest a causal relationship. Due to the retrospective nature of our report and the individual treatment attempt as ultima ratio therapy, a control group without IVIg treatment is lacking. Unresponsiveness in three cases remains unexplained and might indicate variability in pathophysiological mechanisms of encephalopathy. Interestingly, IVIg non-responders presented very high NF-L levels in serum and CSF that might also reflect a more intense neuronal damage leading to a more severe encephalopathy than in responders. Moreover, considering the fatal sepsis development in non-responders, the neurological improvement after IVIg therapy might have been masked by general disease severity with multi-organ failure. Of note, patient #1 started to improve within 1 day after beginning of IVIg treatment, which could be a coincidence. However, a more impressive and, thus, clearly definable improvement was seen 3–4 days after treatment of IVIg, which is why we tend to attribute the clinical change to our therapy.

In conclusion, IVIg are a promising immunotherapy for severe treatment-refractory COVID-19-associated acute encephalopathy. Further prospective controlled studies are required to validate safety and efficacy, monitor long-term outcome, and explore the mechanisms of the therapeutic IVIg effect.

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**Author contributions:** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SH, CF, CF and FS. The first draft of the manuscript was written by SH and CF and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Table 4 Results, primary clinical outcome**

|                       | Before IVIg | After IVIg | Discharge |
|-----------------------|-------------|------------|-----------|
| CAM-ICU               | 78% not possible | 56% not possible | 67% negative |
| CAM-ICU               | 22% positive | 44% positive | 22% positive |
| RASS                  | –3          | –5, 2      | –4, 2     |
| RASS                  | –5, 2       | 0          | 0         |
| GCS                   | 6           | 3, 12      | 5, 14     |
| GCS                   | 3           | 11         | 14.5      |
| GOS                   | 2           | 2, 3       | 2, 3      |
| GOS                   | 3           | 3          | 3         |
| mRS                   | 5           | 4, 5       | 4         |
| mRS                   | 4           | 3, 5       | 3, 5      |
| mRS                   | 5           | 4          | 4         |
| mRS                   | 4           | 3, 5       | N/A       |

CAM-ICU results are “not possible” if RASS is -4 or -5. N/A is stated if patient died before discharge.

CAM-ICU: Confusion Assessment Method for Intensive Care Unit, GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, IVIg: intravenous immunoglobulins, mRS: modified Rankin Scale, N/A: not applicable, RASS: Richmond Agitation–Sedation Scale.
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Data availability  Anonymized data will be shared upon request from any qualified investigator.

Declarations

Conflicts of interest  The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval  All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A Charité-Universitätsmedizin Berlin (EA4/187/021).

Consent to publish  All patients or their legal guardians have consented to the submission of the case report to the journal.

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