

A postmortem case of fulminant anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis with markedly elevated cerebrospinal fluid IL-6: a case report

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Case Report

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Abstract

Background

Anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)

encephalitis is an autoimmune encephalitis with a wide range of clinical manifestations. Underlying conditions should be evaluated on a case-by-case basis, and the pathophysiology of fulminant anti-AMPA encephalitis remains incompletely understood, with very few opportunities for pathological investigation.

Case presentation

An 84-year-old woman developed disorientation to date and place 7 days before admission and was admitted with a fever of 39 °C. On hospital day 3, she developed a decreased level of consciousness, with a Glasgow Coma Scale score of 8, along with tremor and rigidity of the limbs. Brain magnetic resonance imaging revealed bilaterally symmetric lesions in the frontal and temporal cortices and subcortical regions, basal ganglia, and limbic system. Cerebrospinal fluid analysis showed an elevated interleukin-6 level of 3,940 ng/L. Immunotherapy consisting of intravenous methylprednisolone pulse, plasma exchange, and intravenous immunoglobulin was administered for suspected autoimmune encephalitis. Although the cerebrospinal fluid interleukin-6 level decreased to 16.3 ng/L, impaired consciousness did not improve, and cerebral atrophy was observed. Subsequently, high-titer AMPA antibodies were detected in the cerebrospinal fluid. However, the patient died on hospital day 39 from septic shock. Autopsy revealed infiltration of CD8-positive T cells, microglial accumulation, proliferation of reactive astrocytes, and neuronal loss in the hippocampus. No malignant tumors were identified.

Conclusions

Among cases of fulminant AMPA encephalitis, some may exhibit severe inflammation associated with markedly elevated cerebrospinal fluid interleukin-6 levels and prominent CD8-positive T-cell infiltration. Longitudinal assessment of cerebrospinal fluid interleukin-6 levels should be considered to better characterize the disease course.

Background

Anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) encephalitis is an autoimmune encephalitis associated with immune responses against neuronal cell-surface antigens. AMPA antibodies bind to postsynaptic receptors and induce receptor internalization, leading to synaptic dysfunction and a wide range of clinical manifestations, including memory impairment, psychiatric symptoms, and movement abnormalities [1]. A fulminant form may also occur based on the clinical features at onset [2]. We examined possible disease mechanisms based on the autopsy findings of an older woman with fulminant anti-AMPA encephalitis.

Case presentation

An 84-year-old woman who had been independent in her activities of daily living had a remote history of total hysterectomy for cervical cancer approximately 30 years earlier. She had been followed in internal medicine for hypertension and lower-leg edema for 2 years. Seven days before admission, she repeatedly asked her daughter about the date and day of the week. She frequently checked her mobile phone to confirm the date 2 days before admission. She also remarked that a familiar shrine appeared to have an unusual atmosphere. On the day before admission, she passed dark-red stool and was transported to the emergency department at night, where she was found to have a fever of 39°C. Physical examination revealed abdominal distension and lower-leg edema. Neurological examination showed disorientation to date and place, but no other notable abnormalities. At admission, blood tests showed white blood cell count $6.3 \times 10^9/\text{L}$, hemoglobin 93 g/L, platelet count $193 \times 10^9/\text{L}$, prothrombin time-international normalized ratio 1.06, NH_3 24.7 $\mu\text{mol}/\text{L}$, albumin 26 g/L, blood urea nitrogen 13.2 mmol/L (reference range 2.9–7.1), creatinine 107 $\mu\text{mol}/\text{L}$ (reference range 41–70), glutamic oxaloacetic transaminase 29 U/L, glutamic pyruvic transaminase 26 U/L, gamma-glutamyl transpeptidase 59 U/L, and C-reactive protein 8.6 mg/L (reference range < 1.4). Hepatitis B surface antigen was negative, hepatitis C virus antibody was negative, and serological findings for cytomegalovirus and Epstein-Barr virus were consistent with prior infection. Immunoglobulin G (IgG) was 18.49 g/L (reference range 8.61–17.47), Immunoglobulin A was 2.88 g/L, Immunoglobulin M was 0.76 g/L, antinuclear antibody was negative, and anti-mitochondrial M2 antibodies were negative. Anti-thyroid peroxidase antibodies were elevated at 4,600 IU/L (reference range < 3,300), and anti-thyroglobulin antibodies were elevated at 188,000 IU/L (reference range < 19,300). Brain computed tomography (CT) at admission revealed hypodensity in the lateral regions of both putamina and bony thickening in the left skull consistent with fibrous dysplasia. Abdominal CT revealed an irregular liver margin, ascites, a hematoma in the stomach, and dilation of both renal pelvises (Fig. S1; Additional file 1). Blood and urine cultures obtained at admission were negative, and ascitic fluid examination did not reveal findings suggestive of infection. Upper gastrointestinal endoscopy revealed esophageal varices and redness and edema of the gastric mucosa. Beginning on hospital day 2, the patient ceased responding to verbal stimuli. On hospital day 3, the patient's level of consciousness was 8 on the Glasgow Coma Scale, with no eye tracking or speech. The pupillary light reflex and oculoccephalic reflex were preserved. Neurological examination revealed palmomental reflex, intermittent mild rightward ocular deviation, resting tremor in the limbs, and rigidity in the neck and limbs. Electroencephalography (EEG) on hospital day 3 showed generalized delta-band slow waves (Fig. S2A; Additional file 2). Brain magnetic resonance imaging (MRI) on hospital day 4 revealed bilaterally symmetric lesions involving the frontal and temporal cortical and subcortical regions, basal ganglia, and limbic system (Fig. 1A–C). Cerebrospinal fluid (CSF) analysis on the same day showed a mononuclear cell count of $42 \times 10^6/\text{L}$, a polymorphonuclear cell count of $2 \times 10^6/\text{L}$, protein of 5.33 g/L, and glucose of 3.6 mmol/L (serum glucose 4.8 mmol/L). The IgG index was 0.74 (reference range < 0.75), oligoclonal bands were absent, and the CSF interleukin-6 (IL-6) level was elevated at 3,940 ng/L. CSF multiplex polymerase chain reaction (PCR) (LSI Medience, Tokyo, Japan) was negative for *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria*, *Neisseria meningitidis*, Group B Streptococcus,

Streptococcus pneumoniae, cytomegalovirus, enterovirus, herpes simplex virus type I, herpes simplex virus type II, human herpesvirus 6, parechovirus, varicella-zoster virus, and *Cryptococcus*. Panel testing for paraneoplastic neurological syndromes (BML Inc., Tokyo, Japan) was negative for antibodies against amphiphysin (AMPH), CV2, paraneoplastic Ma2 antigen (PNMA2), Ri, Yo, Hu, recoverin, SOX1, titin, Zic family member 4 (zic4), glutamic acid decarboxylase 65 (GAD65), and delta/notch-like EGF-related receptor (Tr / DNER) in all serum samples. Based on the clinical course, autoimmune encephalitis was suspected, and intravenous methylprednisolone pulse (IVMP) therapy was administered. Although tremor and rigidity resolved after IVMP therapy, impaired consciousness did not improve, so plasma exchange (PE) was initiated. Because of impaired consciousness, the patient was unable to clear secretions independently and was transferred to the intensive care unit, where endotracheal intubation was performed. CSF analysis following two courses of IVMP therapy and two sessions of PE showed gradual decreases in cell count and protein levels, as well as a reduction in the CSF IL-6 level. However, EEG after three sessions of PE revealed very low-amplitude fast activity (Fig. S2B), and because the altered level of consciousness did not improve, intravenous immunoglobulin (IVIg) therapy was initiated. Impaired consciousness persisted after completion of IVIg therapy. On hospital day 25, an autoimmune encephalitis panel test (LSI Medience, Mayo Clinic Laboratories, Rochester, MN, USA) performed on a CSF sample showed that AMPAR antibodies were positive in the cell-based assay and exhibited a high titer of 1,024-fold or higher in the immunofluorescence titer assay. All other antibodies (AMPH, anti-glial nuclear antibody type 1 (AGNA-1), anti-neuronal nuclear antibody type 1 (ANNA-1), anti-neuronal nuclear antibody type 2 (ANNA-2), anti-neuronal nuclear antibody type 3 (ANNA-3), contactin-associated protein-like 2 (CASPR2), collapsin response mediator protein 5 (CRMP5), dipeptidyl-peptidase-like protein 6 (DPPX), gamma-aminobutyric acid B receptor (GABA-B), GAD65, glial fibrillary acidic protein (GFAP), metabotropic glutamate receptor 1 (mGluR1), IgLON5, leucine-rich glioma-inactivated 1 (LGI1), Neurochondrin, neuronal intermediate filament (NIF), N-methyl-D-aspartate receptor (NMDA-R), Purkinje cell cytoplasmic antibody type Tr (PCA-Tr), Purkinje cell cytoplasmic antibody type 1 (PCA-1), Purkinje cell cytoplasmic antibody type 2 (PCA-2), phosphodiesterase 10A (PDE10A), Septin-7, tripartite motif-containing protein 46 (TRIM46)) were negative.

Meanwhile, on hospital day 23, *Enterococcus faecium* and *Candida albicans* were detected in a urine culture, and antibiotic therapy was initiated. On hospital day 25, the β -D-glucan level was 16.6 ng/L, below the reference cutoff of 20 ng/L, so antifungal therapy was not administered. Brain MRI on hospital day 30 showed persistent lesions in the limbic system, including the hippocampus, whereas generalized cerebral atrophy was observed predominantly in the frontal lobes where the previous lesions had resolved (Fig. 1D–F). However, because there was no clear clinical evidence of benefit from immunotherapy and there was concern about worsening infection, no additional immunotherapy for autoimmune encephalitis was administered. The patient died on hospital day 39 from septic shock. On the same day, the β -D-glucan level was 237 ng/L, and *Candida glabrata* was identified in blood cultures (Fig. 2).

At autopsy, the brain weighed 931 g and showed cerebral atrophy. Numerous CD8-positive lymphocytes infiltrated the hippocampus, with perivascular cuffing around small blood vessels. No CD20- or CD79a-

positive cells were observed. GFAP-positive cells were enlarged and increased in number, consistent with reactive astrocytes. Numerous CD68-positive cells were also observed, suggesting microglial accumulation. Neuronal nuclei (NeuN) staining of neuronal cell bodies was reduced, suggesting neuronal loss (Fig. 3). In the kidneys, periodic acid-Schiff staining revealed hyphae-like structures in the renal pelvis, indicating fungal infection; fungal pyelonephritis was considered the direct cause of death (Fig. S3; Additional file 3). No abscesses, neutrophil-predominant inflammation, or vascular wall infiltration suggestive of fungal infection were observed in the brain. The liver showed no bridging fibrosis or pseudolobulation suggestive of cirrhosis; instead, nodular regenerative hyperplasia (NRH) and dilation of sinusoids in the central zones of the lobules were observed (Fig. S3; Additional file 3). Findings suggestive of portal hypertension, including gastric varices, were present during life. Comprehensive evaluation and exclusion of other diseases with overlapping pathological features supported a clinical diagnosis of porto-sinusoidal vascular disease (PSVD). Systemic examination revealed no tumors. Although anti-thyroid antibodies had been positive during life, no thyroid enlargement was observed.

Discussion and Conclusions

α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are ionotropic glutamate receptors that mediate excitatory neurotransmission. They are tetramers composed of GluA1 to GluA4 subunits in varying combinations and are widely distributed throughout the brain, including the limbic system, cerebral cortex, basal ganglia, cerebellum, and brainstem, with region-specific differences in subunit composition [3]. In anti-AMPA receptor encephalitis, AMPAR antibodies induce internalization and loss of AMPA receptors from the synaptic surface [2], resulting in decreased AMPA receptor-mediated synaptic currents, reduced inhibitory synaptic transmission, and increased neuronal excitability, leading to diverse neurological dysfunction [4].

Cell-based assays, which have high sensitivity and specificity, are recommended for detecting AMPA receptor antibodies [5], and testing can be performed using serum, CSF, or both [6]. AMPA receptor antibodies may target GluA1 or GluA2, with GluA2 antibodies being more common. Although the antibody subtype was not evaluated in this case, clinical presentation does not appear to differ clearly between the two subtypes [7]. In this case, the AMPA receptor antibody titer was 1,024-fold or higher by the immunofluorescence titer assay. However, no diagnostic titer threshold has been established for AMPA receptor antibody positivity, and a positive correlation between elevated antibody titers and disease severity has not been established [8].

Symptoms of anti-AMPA receptor encephalitis include recent memory impairment (80.3%), psychiatric symptoms (80.3%), altered consciousness (77.3%), motor abnormalities (37.9%), seizures (28.8%), disorientation (19.7%), aphasia (12.1%), insomnia (10.6%), and autonomic symptoms (9.1%) [9]. Joubert et al. classified anti-AMPA receptor encephalitis into four main clinical forms based on the predominant presentation at admission: confusion, epileptic, pure amnesic, and fulminant encephalitis. The fulminant form typically evolves from one of the other forms and is characterized by acute loss of consciousness,

fever, diffuse hypertonia, and lateralized ocular deviation [2]. Given these features, we considered this patient to have the fulminant form. However, anti-AMPA encephalitis also includes cases in which motor symptoms, ataxia, or aphasia are initial manifestations [7]. Cases similar to ours, with acute progression to impaired consciousness or coma and described as fulminant or severe, have been reported sporadically [2, 4, 10–14] (Additional file 4). Among these cases, neuroimaging findings are heterogeneous: some show widespread cortical and subcortical lesions [2, 10, 11] similar to those in this case, whereas others show lesions confined to the temporal lobes [12], cerebellum [13], or striatum [2], and still others show no radiologic abnormalities suggestive of encephalitis [14]. A similar discordance between imaging findings and disease severity is observed in other forms of autoimmune encephalitis [15], and imaging findings alone therefore cannot determine disease severity in anti-AMPA encephalitis. In addition, the mechanisms underlying clinical deterioration in anti-AMPA encephalitis remain unclear.

Several cytokines are being evaluated as biomarkers for autoimmune encephalitis. Interleukin-6 (IL-6) is an inflammatory cytokine produced by immune cells such as T cells and microglia and by nonimmune cells such as neurons and astrocytes [16, 17].

CSF IL-6 levels may be elevated nonspecifically in central nervous system disorders, including infection [18], lymphoma [19], neuromyelitis optica spectrum disorder [20], N-methyl-D-aspartate receptor encephalitis [18], and leucine-rich glioma-inactivated 1 (LGI1) encephalitis [21]. Studies of autoimmune encephalitis have shown that lower post-treatment CSF IL-6 levels are associated with a better prognosis and may serve as an indicator of disease severity and progression [22]. In this case, although CSF cell counts and protein levels decreased following immunotherapy, these changes were not accompanied by improvement in the patient's level of consciousness.

Before immunotherapy, the CSF IgG index was not elevated and oligoclonal bands were absent, suggesting that intrathecal B-cell clonal proliferation may not have been a dominant mechanism. Notably, this case was characterized by markedly elevated CSF IL-6 levels. Potential IL-6-associated effects, including enhanced CD8-positive T-cell differentiation and cytotoxic activity, amplification of central inflammation through microglial activation [23], and astrocyte hypertrophy and proliferation through signal transducer and activator of transcription 3 signaling [24], were broadly consistent with the postmortem pathological findings. These findings suggest that markedly elevated IL-6 may have contributed to a severe inflammatory process associated with progression to fulminant anti-AMPA encephalitis and irreversible cerebral atrophy. Studies of LGI1 encephalitis have reported a higher incidence of recurrence among patients with elevated IL-6 levels [21], suggesting that longitudinal monitoring of IL-6 may warrant further evaluation even after stabilization of autoimmune encephalitis. Further studies are needed to clarify the role of IL-6 and other cytokines in the pathophysiology of anti-AMPA encephalitis.

In this case, the neurological antibody panel evaluated for paraneoplastic syndromes was negative, and no tumor was found on systemic examination at autopsy. The trigger for anti-AMPA encephalitis remained unknown. Autopsy findings revealed NRH and dilated hepatic sinusoids. The diagnosis of

PSVD can be established by excluding other conditions with similar pathological features, such as intra- or extrahepatic portal vein obstruction, autoimmune hepatitis, congestive hepatopathy, hematologic disorders, and chronic infections. PSVD is proposed as a form of hepatic vascular disease without cirrhosis, regardless of the presence or absence of portal hypertension [25]. PSVD has been reported in association with systemic lupus erythematosus, inflammatory bowel disease, and primary immunodeficiency disorders, suggesting possible involvement of immune mechanisms. Vascular endothelial damage and microcirculatory dysfunction are also considered central to its pathophysiology [26]. However, no relationship between PSVD and encephalitis has been established, and its role as an underlying condition in this patient remains unclear.

At autopsy, no thyroid enlargement was observed, and the premortem history was not suggestive of Hashimoto's encephalopathy (HE). However, a previous report described AMPAR encephalitis occurring concurrently with HE in the context of thyroid autoimmunity [27]. It remains unclear whether the anti-thyroid antibodies in this patient reflected an underlying immunologic predisposition.

In late-onset autoimmune encephalitis, even when no underlying condition such as a tumor is identified, multiple factors, including age-related immune alterations [28, 29] and genetic factors such as human leukocyte antigen type [30], may contribute to disease development, supporting case-by-case evaluation of the underlying pathophysiology. Further investigation is also required to clarify the factors associated with the markedly elevated CSF IL-6 level.

Although CSF IL-6 could not be measured at autopsy in this case, the pathological findings were compatible with inflammatory changes that may occur in the setting of markedly elevated CSF IL-6. Given the diverse clinical manifestations of anti-AMPA encephalitis, serial measurement of CSF IL-6 from an early stage, even before a definitive diagnosis is established, may be useful for monitoring disease activity.

Abbreviations

AGNA-1

Anti-glial nuclear antibody type 1

AMPA

α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AMPA

α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

AMPH

Amphiphysin

ANNA-1/Hu

Anti-neuronal nuclear antibody type 1

ANNA-2/Ri

Anti-neuronal nuclear antibody type 2

ANNA-3
Anti-neuronal nuclear antibody type 3
CASPR2
Contactin-associated protein-like 2
CD8
Cluster of differentiation 8
CD20
Cluster of differentiation 20
CD68
Cluster of differentiation 68
CD79a
Cluster of differentiation 79a
CRMP5/CV2
Collapsin response mediator protein 5
CSF
Cerebrospinal fluid
CT
Computed tomography
DNER/Tr
Delta/notch-like epidermal growth factor-related receptor
DPPX
Dipeptidyl-peptidase-like protein 6
EEG
Electroencephalography
FLAIR
Fluid-attenuated inversion recovery
GABA-B
Gamma-aminobutyric acid B receptor
GAD65
Glutamic acid decarboxylase 65
GFAP
Glial fibrillary acidic protein
GluA1-GluA4
AMPA receptor subunits 1–4
HE
Hashimoto's encephalopathy
IgG
Immunoglobulin G
IgLON5
Neuronal cell adhesion molecule

IL-6
Interleukin-6
IVIg
Intravenous immunoglobulin
IVMP
Intravenous methylprednisolone pulse
LGI1
Leucine-rich glioma-inactivated 1
mGluR1
Metabotropic glutamate receptor 1
MRI
Magnetic resonance imaging
NeuN
Neuronal nuclei
NIF
Neuronal intermediate filament
NMDA-R
N-Methyl-D-aspartate receptor
NRH
Nodular regenerative hyperplasia
PCA-1/Yo
Purkinje cell cytoplasmic antibody type 1
PCA-2
Purkinje cell cytoplasmic antibody type 2
PCA-Tr
Purkinje cell cytoplasmic antibody type Tr
PCR
Polymerase chain reaction
PDE10A
Phosphodiesterase 10A
PE
Plasma exchange
PNMA2
Paraneoplastic Ma2 antigen
PSVD
Porto-sinusoidal vascular disease
SOX1
SRY-box transcription factor 1
TRIM46
Tripartite motif-containing protein 46

Declarations

Ethics approval and consent to participate

According to the institutional policy of Takatsuki General Hospital, post-mortem single-case reports, including autopsy findings, are not subject to institutional ethical review and do not constitute human subject research. Although this report involves human tissue, it does not involve human participants or human data in a manner that meets the definition of human subject research. Therefore, this case report was not submitted to the Institutional Review Board of Takatsuki General Hospital, and no reference number was assigned. As this report does not involve human participants or human subject research, the Declaration of Helsinki is not applicable.

Consent for publication

Autopsy was performed with permission from the patient's family. As the patient was deceased, written informed consent for publication of this case report and its accompanying clinical information and medical images was obtained from the patient's eldest daughter, who was the patient's next of kin.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

HT collected the clinical data, reviewed the medical records, and drafted the manuscript. TO performed the neuropathological examination and interpreted the histopathological findings. TM revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data Availability

All data generated or analyzed during this case report are included in this published article. No additional datasets are available.

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Figures

Fig.1

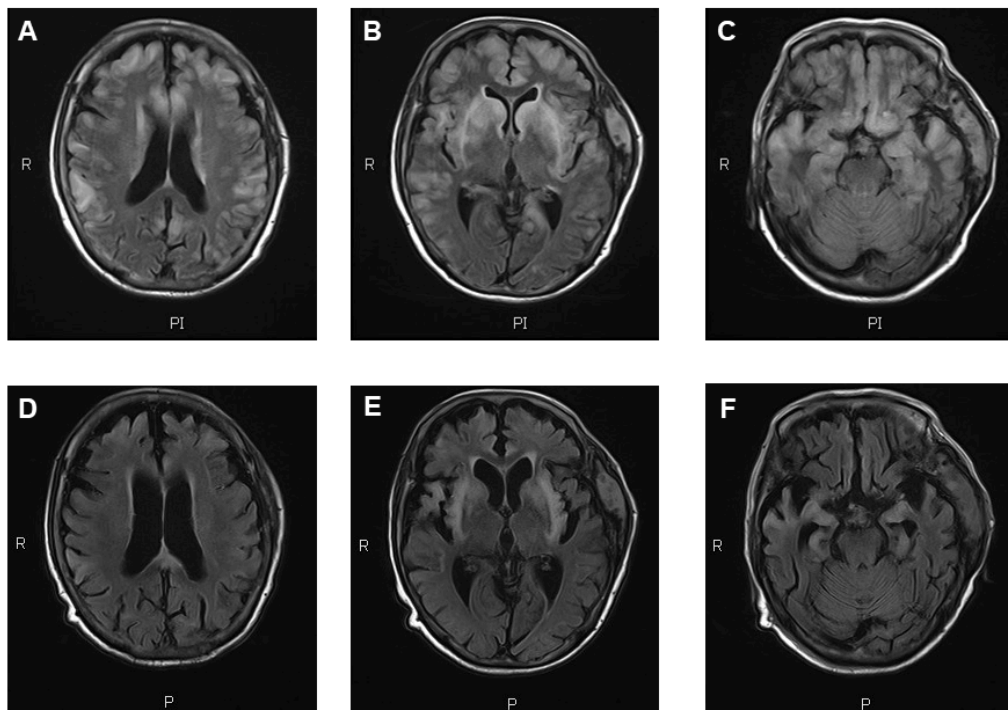


Figure 1

Serial brain FLAIR findings on hospital days 4 and 30

Fluid-attenuated inversion recovery (FLAIR) images obtained on day 4 showing bilaterally symmetric hyperintense lesions involving the cortical and subcortical regions of the frontal and temporal lobes, basal ganglia, and limbic system (A-C).

FLAIR images obtained on day 30 demonstrating persistent lesions in the limbic system, including the hippocampus, and generalized cerebral atrophy predominantly in the frontal lobes where the previous lesions had resolved (D-F).

Fig. 2

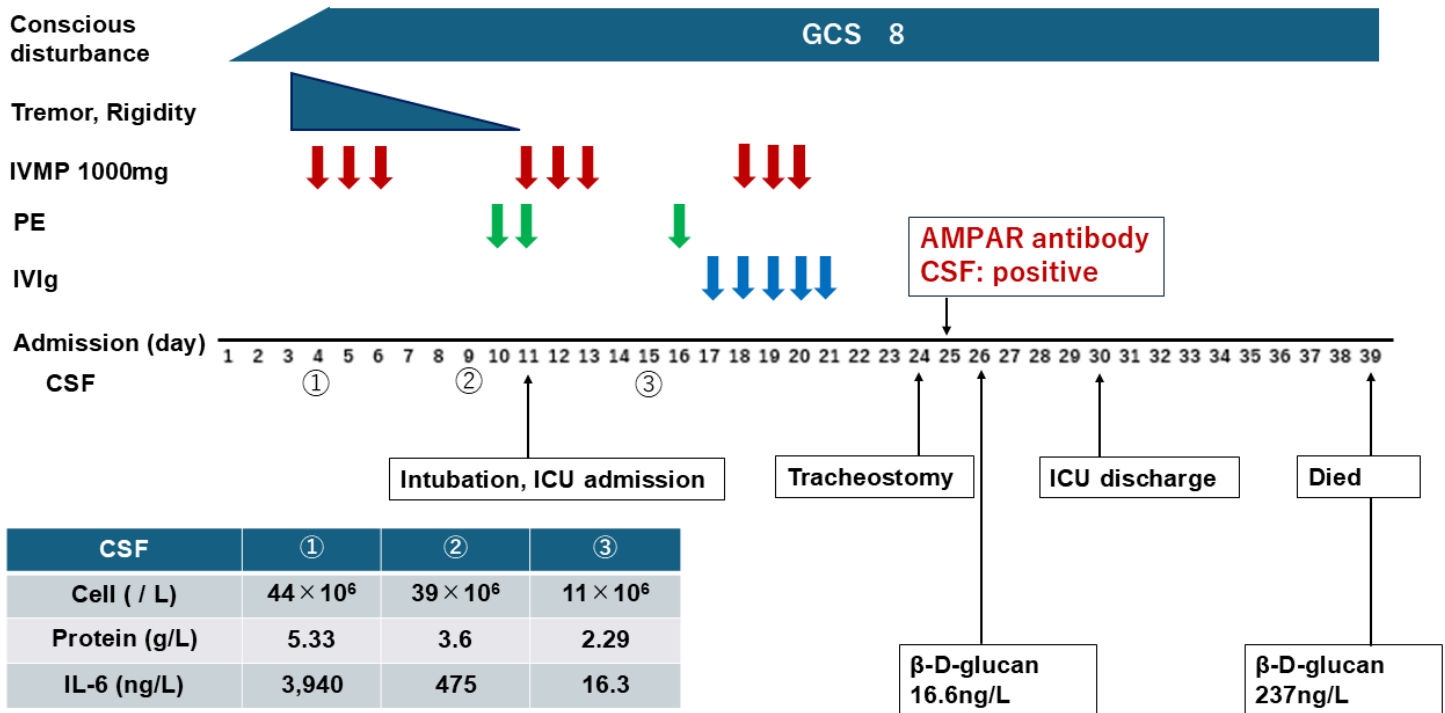


Figure 2

Clinical course and cerebrospinal fluid (CSF) findings, including interleukin-6 (IL-6) levels.

Clinical course illustrating the timing of immunotherapies and numbered CSF sampling points. The first course of IVMP was administered on Days 4–6, the second on Days 11–13, and the third on Days 18–20. PE was performed on Days 10, 11, and 16, followed by IVIg on Days 17–21. CSF was sampled on Days 4, 9, and 15, corresponding to the numbered circles. The patient died on Day 39.

Fig. 3

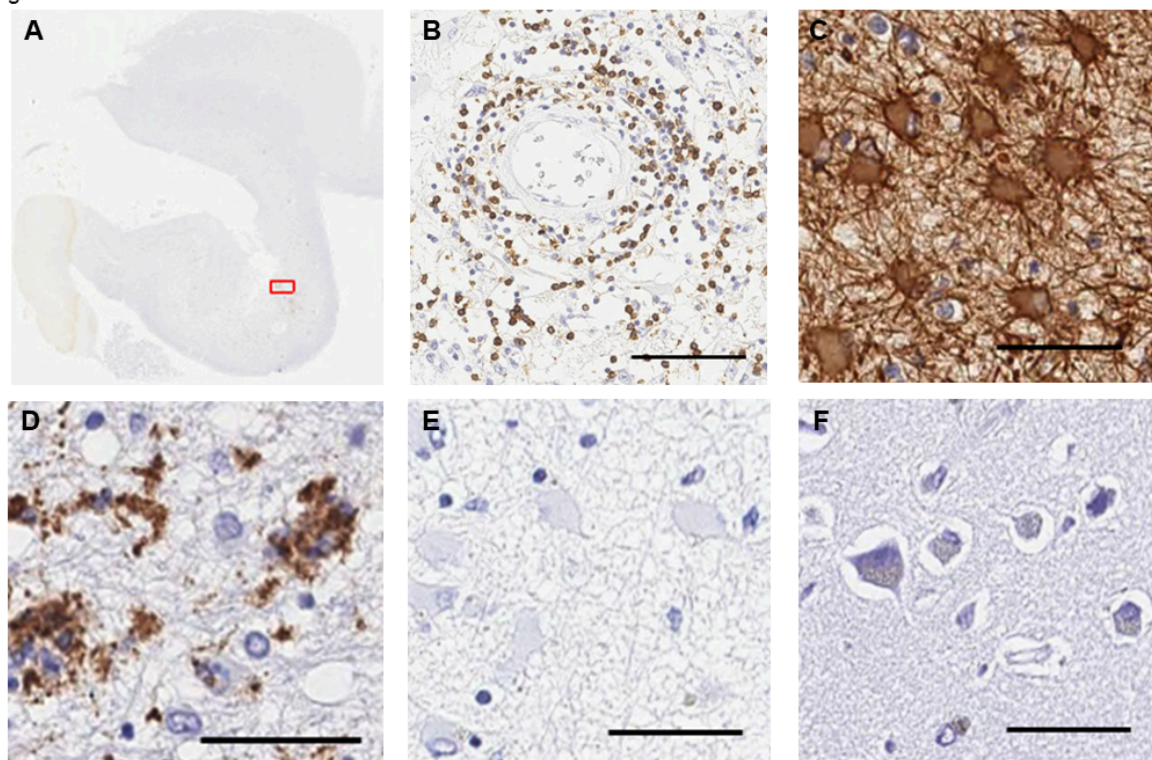


Figure 3

Histopathological findings of the right hippocampus.

The red rectangle in A indicates the area enlarged in B. Numerous CD8-positive lymphocytes infiltrate the hippocampus with prominent perivascular cuffing (B). GFAP-positive astrocytes are enlarged and increased in number (C). Abundant CD68-positive cells suggest microglial accumulation (D). NeuN staining is markedly diminished in the right hippocampal lesion (E), whereas the ipsilateral temporal neocortex shows relatively preserved NeuN staining as an internal reference (F).

Scale bars: 100 μ m in B and 50 μ m in C-F.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1.pptx](#)
- [Additionalfile2.pptx](#)
- [Additionalfile3.pptx](#)
- [Additionalfile4.xlsx](#)