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Acute haemorrhagic necrotizing encephalopathy and inflammatory demyelinating encephalopathy associated with COVID-19 in adults in Southern China

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Abstract

Background COVID-19 manifests with diverse systemic symptoms, including central nervous system involvement. Acute necrotizing encephalopathy (ANE), acute hemorrhagic leukoencephalitis (AHLE), and acute disseminated encephalomyelitis (ADEM) exhibit overlapping clinical features, creating diagnostic challenges. This study characterizes COVID-19-associated neuroinflammatory syndromes in patients without apparent respiratory symptoms.

Methods We conducted a retrospective case series analysis of four patients with confirmed COVID-19 and acute neurological decline. Diagnostic evaluation included brain MRI, cerebrospinal fluid analysis, autoimmune/paraneoplastic antibody panels, and exclusion of alternative etiologies through microbiological/metabolic testing.

Results Four cases were identified: two with ANE, one with ADEM, and one with AHLE. All patients tested SARS-CoV-2-positive by RT-PCR despite absent respiratory symptoms. Magnetic resonance imaging revealed characteristic patterns: Symmetric thalamic lesions in ANE (Cases 1–2), hemorrhagic lesions in basal ganglia and bilateral cerebellar hemispheres in AHLE (Case 3), widespread cortical and subcortical demyelination in ADEM (Case 4).

Conclusions ANE, AHLE, and ADEM are critical neuroinflammatory complications of COVID-19 requiring urgent differentiation. It is imperative to maintain a high level of clinical suspicion when patients present with acute encephalopathy in the absence of respiratory symptoms, as this enables timely intervention.

Keywords Acute necrotizing encephalopathy, Acute hemorrhagic leukoencephalitis, Acute disseminated encephalomyelitis, Coronavirus, COVID-19

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Introduction

Neurological complications of COVID-19 present with diverse clinical manifestations, including ischaemic events, posterior reversible encephalopathy syndrome, encephalopathy, encephalitis, encephalomyelitis, myelitis, neuritis and Guillain–Barré syndrome [1–4]. Acute demyelinating encephalitis or encephalopathy associated with COVID-19 are rare but exhibit striking manifestations [4–6]. This complication does not appear to be correlated with the severity of respiratory symptoms related to COVID-19 and may result from immune reactions to viral infection and a yet-to-be-elucidated cytokine storm syndrome [7, 8]. Demyelinating encephalopathy linked with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) carries a high rate of morbidity and mortality but is less frequently reported [6, 9]. There is limited documentation regarding neurological symptoms as initial indicators of COVID-19. Notably, neurological complications may arise even in the absence of significant respiratory symptoms, highlighting the necessity for a heightened level of suspicion to facilitate early diagnosis. In this report, we describe four cases of acute encephalopathies without respiratory manifestations in our experience with COVID-19. These cases include two instances of acute necrotizing encephalopathy (ANE), one case of acute haemorrhagic leukoencephalitis (AHLE) and one case of acute disseminated encephalomyelitis (ADEM) encountered among 129 patients with COVID-19 infection. Consistent with sporadic reports and small case series during the pandemic, our patients tested negative for neural immunoglobulin G (IgG) and cerebrospinal fluid (CSF) viral particles.

Subjects and methods

All patients diagnosed with ANE and acute inflammatory demyelinating encephalopathy associated with COVID-19 were recruited from the Mental and Neurological Diseases Research Center, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, South China. Subjects who were seen during the period between 01/12/2022 and 01/04/2023 were recruited. The research was conducted in accordance with the Declaration of Helsinki and approval was obtained from the Institutional Ethics Committee of The Third Affiliated Hospital of Sun Yat-Sen University(ethical number: CR2023-011-01). The study included patients with confirmed SARS-CoV-2 infection by nasopharyngeal reverse transcription polymerase chain reaction(RT-PCR), new-onset neurological symptoms suggestive of encephalopathy or encephalitis, and MRI findings consistent with ADEM, ANE, or AHLE [6–9]. All patients underwent a comprehensive evaluation by experienced neurologists to exclude other infective, autoimmune, or metabolic causes of encephalopathy. Patients were excluded if they had pre-existing neurological disorders that could explain the clinical or imaging findings or lacked confirmatory SARS-CoV-2 testing. Subjects were actively recruited in this study by two experienced neurologists from the Department of Neurology. Demographics, clinical manifestations at onset and the course of the patients during their stay were directly obtained and recorded.

Magnetic resonance imaging (MRI) results were obtained, along with CSF studies, autoimmune profiles and microbiological tests and relevant examinations. Brain MRI was conducted using a Siemens MAGNETOM Lumina 3T system (Siemens Healthineers, Erlangen, Germany), with an imaging protocol that incorporated conventional T1-weighted sequences, gadolinium contrast-enhanced T1-weighted sequences, T2-weighted sequences (T2W) and T2 fluid-attenuated inversion recovery (T2 FLAIR), susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI), magnetic resonance angiography and magnetic resonance venography. CSF analysis was performed in these four patients and included CSF cell count, total protein levels, glucose levels, chloride levels, oligoclonal bands (OCB) and comprehensive pathogen detection using metagenomic next-generation sequencing (mNGS). The autoimmune encephalitis (AIE) panel, inflammatory demyelinating antibodies and paraneoplastic antibody panel were detected in patients' CSF and serum samples through cell-based assay done by KingMed Diagnostic Company (Guangzhou, Guangdong, China). The AIE panel included N-methyl D-aspartate, voltage-gated potassium channel, and gamma-aminobutyric acid, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antibodies, immunoglobulin-like cell adhesion molecule 5, dipeptidylpeptidase-like protein-6, glyoxylate reductase 1, dopamine 2 receptor, glutamic acid decarboxylase 65, metabotropic glutamate receptor 1 and contactin-associated protein-like 2. The inflammatory demyelinating antibodies included aquaporin-4 (AQP4)-IgG, myelin oligodendrocyte glycoprotein (MOG)-IgG, and glial fibrillary acidic protein-IgG. The paraneoplastic antibody panel included ZiC4, Tr/Delta/notch-like epidermal growth factor-related receptor, SOX-1, Ma1, Ma2, CV2/collapsin response mediator protein 5, Amphiphysin, Hu/antineuronal nuclear antibody-1, Ri/antineuronal nuclear antibody-2, and Yo/Purkinje cell antibody-1. Microbiological evaluation also included blood and CSF cultures, serological and/or secretional tests for influenza, syphilis, hepatitis, tuberculosis and human immunodeficiency virus. And systemic inflammatory markers, including interleukin-6 (IL-6), C-reactive protein, and procalcitonin, along with all relevant connective tissue disease (CTD)-associated autoantibodies, were comprehensively screened. Various treatments given to the patients along with their responses to therapies were also recorded.

Observations and results

Patient presentation and workup

Clinical manifestation, diagnostic feature including CSF findings during hospital management and final outcome of patients were shown in Table 1. The initial laboratory work-up was negative for influenza, with the diagnosis of COVID-19 made by detection of SARS-CoV-2 via a viral nucleic acid assay by RT-PCR. The assay was performed using a Cobas Z 480 analyser (Roche, cobas z 480 analyzer, Basel, Switzerland) at our institution following emergency use authorization from the U.S. Centers for Disease Control and Prevention. The mNGS testing for the cerebrospinal fluid was performed and SARS CoV-2 was not found in the CSF. And all autoantibodies of AIE, inflammatory demyelinating disease and paraneoplastic symdrone were negative in serum or CSF samples. The time interval between COVID-19 positive test positive test of RT-PCR and neurological onset ranged from 1 day to 28 days. The subsequent section and Table 1 provide a comprehensive elucidation of the clinical presentation and progression of patients.

Table 1 Characteristics of 4 patients with central neurvous system inflammatory disorders with SARS-CoV-2 infection

Patient number	Patient 1	Patient 2	Patient 3	Patient 4
Age	25	23	35	52
Sex	Female	Male	Male	Female
Time interval from SARS-CoV-2 (+) to neurologic onset	1d	3d	15d	28d
Level of consciousness	Coma (GCS 9, E3,V2,M4)	Delirium (GCS 13, E4,V4, M5)	Coma (GCS 8, E2,V1, M5)	Delirium (GCS 11, E4, V2, M5)
Previous medical history	Healthy	Healthy	Lymphoma	Healthy
Involved lesions in MRI	Bilateral thalami, pons and bilateral cerebellum	Bilateral thalamus, pons and left cerebellum	Bilateral parieto-occipito-temporal and left frontal and periventricular white matter	Bilateral frontoparietal temporal lobe, left cerebellum and right brachium of pons
CSF	RBCs 1/mm^3 WBCs 30/mm^3 (92%lym) Pro 80.5 mg/dl Glu 5.66 mmol/L Chlorine 127mmol/L OCB(-)	None	RBCs 560/mm^3 WBCs 50/mm^3 (10%lym) Pro 84 mg/dl Glu 3.52 mmol/L Chlorine 132 mmol/L OCB(-)	RBCs 0 WBCs 50/mm^3 Pro 48 mg/dl Glu 3.34 mmol/L Chlorine 127 mmol/L OCB(-)
Immune therapy	IVMP + IVIG+ tocilizumab	IVMP	IVMP + IVIG	IVMP + IVIG
Diagoses	ANE	ANE	AHLE	ADEM
mRS at admission	5	3	5	4
mRS at discharge	5	2	6	3
Residual neurological dysfunction	Bulbar paralysis, dementia, quadriplegia	Cognitive impairment (MMSE 15)	Dead	Cognitive impairment, mild paresis

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; *GCS* glasgow coma scale; *MRI* magnetic resonance imaging; *CSF* cerebrospinal fluid; *RBCs* Red blood cells in CSF; *WBCs* white blood cells in CSF; *Pro* proteins; *ANE* acute necrotizing encephalopathy; *AHLE* acute hemorrhagic leukoencephalitis; *ADEM* acute disseminated encephalomyelitis; *IVMP* intravenous methylprednisolone; *IVIG* intravenous immunoglobulin; *mRS* modified rankin scale; *MMSE* mini-mental state examination

Clinical presentations and progress

Patient 1

A 25-year-old female teacher presented with a fever of 39.1 °C and a decreased level of consciousness (GCS9: E3,V2,M4) that occurred within 24 h. She tested positive for SARS-CoV-2 on nasopharyngeal swabs. CSF analysis showed an increased protein level (80.5 mg/dl) without pleocytosis, and mNGS for pathogens and for SARS-CoV-2 were negative in the CSF. In the serum, the IL-6 levels were in the normal range, and central nervous system (CNS) autoantibodies, including MOG-IgG, AQP4-IgG and paraneoplastic antibody panels and antibodies against AIE, were absent. The search for OCB in CSF and serum was negative. Brain MRI demonstrated haemorrhagic rim-enhancing lesions within the bilateral thalami, pons and bilateral cerebellar hemisphere, and left centrum semiovale and lateral paraventricular region (Fig. 1). The patient received two rounds of intravenous immunoglobulin(Sichuan Yuanda Yang Pharmaceutical Co., LTD, Shuyang, Chengdu, Sichuan, China) and high-dose steroids(Liaoning sea cisco pharmaceutical co., LTD, Siwu, Xingcheng, Liaoning, China). She also received tocilizumab (Chugai Pharma Manufacturing Co., Ltd., Actemra, Tockyo, Japan) therapy. The patient presented with an modified rankin scale (mRS) score of 5 before treatment and showed no improvement after one month, remaining at an mRS score of 5 with persistent bulbar paralysis, dementia and quadriplegia.

Patient 2

A 23-year-old male was admitted with fever for 1 day and then behavioural and psychological symptoms for ten days. The patient could not cooperate with the cognitive assessment on admission. SARS-CoV-2 RNA PCR was positive on throat swabs. MRI of the brain revealed asymmetric bilateral T2W and FLAIR hyperintensities

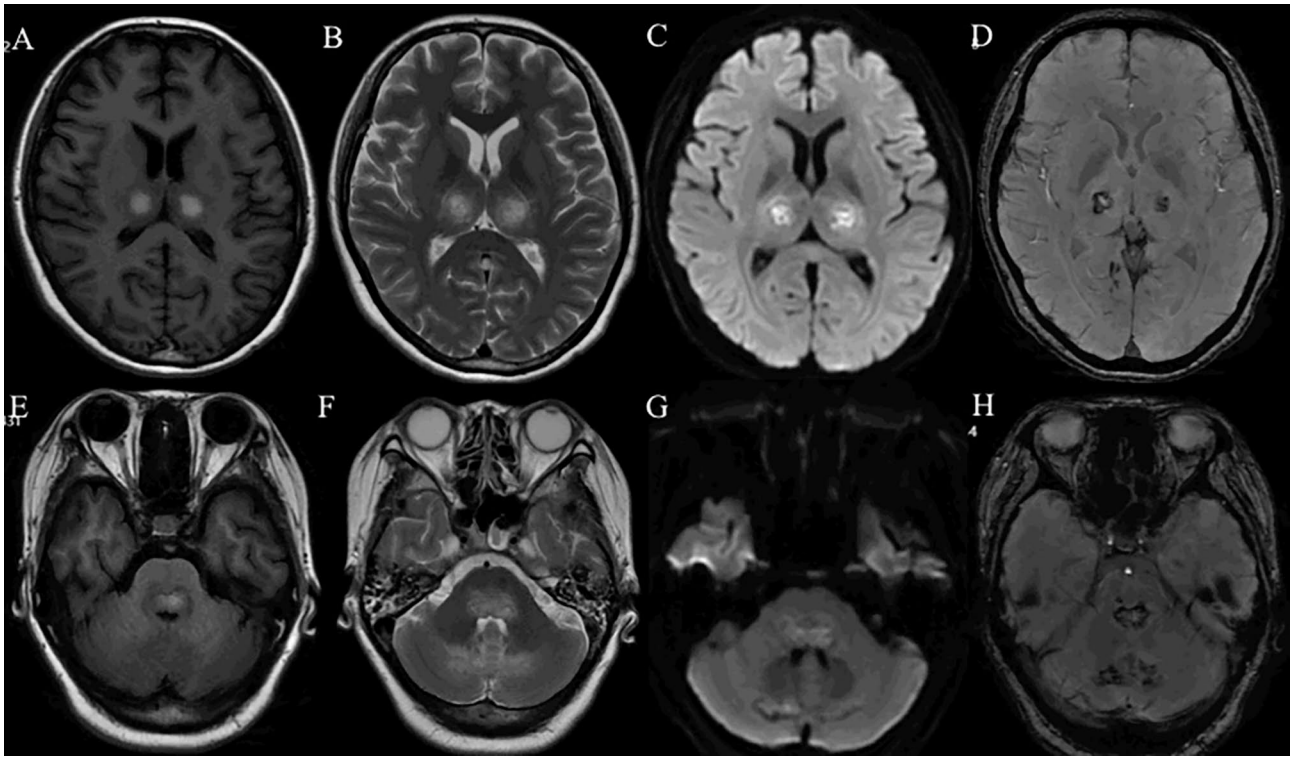

Fig. 1 Patient 1 Acute necrotizing encephalopathy in a 25-year-old girl presenting with fever and consciousness disturbance. Axial FLAIR (**B** and **F**) and (**C** and **G**) T2-weighted images show hyperintensities in the bilateral thalami, PONS, and bilateral cerebellar hemisphere. Axial T1-weighted image (**A** and **E**) reveals hyperintensities, suggesting haemorrhages in the thalami and pons. **D** and **H** SWI image demonstrating cerebral microbleeds in the bilateral thalami and bilateral cerebellar hemisphere

in the bilateral thalamus, pons, and left cerebellum, with areas of haemorrhages and no areas of enhancement (Fig. 2). The patient could not cooperate with lumbar puncture even under sedation. He received a course of intravenous methylprednisolone succinate (IVMP) (Liaoning sea cisco pharmaceutical co., LTD, Siwu, Xingcheng, Liaoning, China), 1 g daily for 3 days and 0.5 g daily for 2 days, with only moderate improvements in his cognitive function. The patient had an mRS score of 3 prior to treatment and improved to a score of 2 post-treatment, though he remained lethargic with impaired memory, apathy, and mental disturbances. His cognitive deficits were evident, with a Mini-Mental State Examination (MMSE) score of 15/30 at discharge.

Patient 3

A thirty-five-year-old male presented with loss of consciousness for 5 days. There was an episode of intermittent headache and fever for 20 days prior to coma, hyperspasmia and other encephalopathy symptoms. He tested positive for SARS-CoV-2 by RT-PCR at 15 days before getting an acute impaired consciousness. He received intravenous immunoglobulin (IVIG) 0.4 g/kg. D, acyclovir and antibiotics at a local hospital without any clinical improvement. Examination showed GCS8 (E2, V1, M5) at admission in our department. Workups to look for immunological diseases, including anti-nuclear antibody blot, anti-neutrophil cytoplasmic antibody, AQP4 and MOG antibody, paraneoplastic antibody panel and AIE panel, were all negative. CSF analysis showed 50 cells/cu mm (neutrophils 70%, monocytes 20% and lymphocytes 10%) with increased protein at 84 mg/dl. CSF pathogen sequencing was negative. MRI of the brain showed multiple ill-defined areas of altered signal intensity involving bilateral parieto-occipito-temporal and left frontal periventricular white matter with haemorrhages (Fig. 3A). Critically, he suffered an increase in oedema, inducing a right subfalx hernia and cerebellar tonsil hernia (Fig. 3B). We started an IVMP((Liaoning sea cisco pharmaceutical co., LTD, Siwu, Xingcheng, Liaoning, China) pulse immediately and continued IVMG(Sichuan Yuanda Yang Pharmaceutical Co., LTD, Shuyang, Chengdu, Sichuan, China) combined with a full dose of dehydrating drugs(Shanghai Baxter Medical Supplies Co., LTD, 25% mannitol injection, Shanghai, China; Henan Runhong Pharmaceutical Co. LTD, Furosemide injection, Henan, China and Huaxia Shengsheng Pharmaceutical Co. LTD, Glycerin fructose and sodium chloride injection, Beijing, China) and advanced antibiotics(Sumitomo pharmaceuticals co., LTD, Mepem,

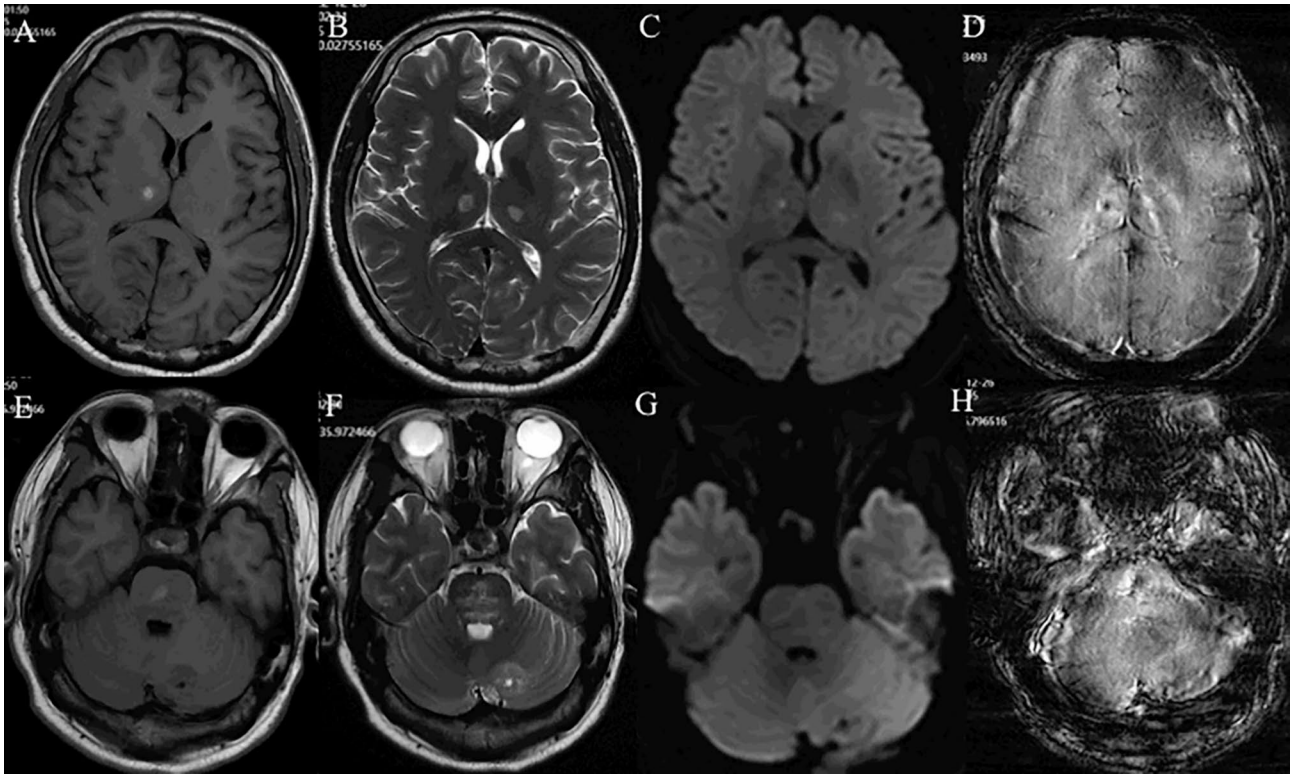

Fig. 2 Patient 2 Acute necrotizing encephalopathy in a 23-year-old male presenting with mental disorders. Axial T2-weighted (**B** and **F**) and T2 FLAIR (**C** and **G**) images show hyperintensities in the bilateral thalami and pons. Axial T1-weighted image (**A** and **E**) reveals hyperintensities, suggesting haemorrhages in the right thalami and pons. **D** and **H** SWI image demonstrating cerebral microbleeds in the right thalamus

Suzhou, jiangsu, China; and Hunan Kelun Pharmaceutical Co., LTD, zyvoxid, Hunan, China). However, Patient 3 soon underwent intubation and mechanical ventilation due to progressive worsening. Then, he succumbed on the second day of admission, with mRS score changed from 5 to 6.

Patient 4

A 52-year-old female was admitted with dizziness and subsequent cognitive and mental disorders for 2 weeks. She had a history of fever and headache 6 weeks prior and was SARS-CoV-2 positive 4 weeks before manifesting neurological disorders. The patient had persistent delirium with stable vital signs. CSF analysis showed 50 cells/cu mm (neutrophils 70%, monocytes 20% and lymphocytes 10%) with increased protein at 84 mg/dl. Head MRI demonstrated multiple asymmetric lesions in the bilateral frontoparietal temporal lobe, left cerebellar hemisphere and right brachium of the pons, with severe vasogenic oedema in the frontal and parietal regions. These lesions had leading edges on contrast imaging, and without haemorrhage proven by SWI, a diagnosis of ADEM was made. Brain MRI showed bilateral white matter changes (Fig. 4A–H). The electroencephalography (EEG) findings of Patient 4 revealed moderate to severe abnormalities which showed predominant theta activity in the frequency range of 4–7 Hz with amplitudes between 30 and 60 μV. And there was a slight increase in alpha activity at 8–10 Hz (20–50 μV). Additionally, mild diffuse low-amplitude beta activity was observed within the 14–22 Hz range. Scattered delta waves, occurring at 2–3 Hz with amplitudes of 30–60 μV, were also noted, no clear epileptiform discharges were observed. The EEG images are provided in Supplementary File. There was slow and still ongoing neurological improvement over 4 weeks with first-line immunotherapy with three rounds of high-dose intravenous methylprednisolone (1 g daily for a total of 11 days) (Liaoning sea cisco pharmaceutical co., LTD, Siwu, Xingcheng, Liaoning, China) and 5 days of IVIG(Sichuan Yuanda Yang Pharmaceutical Co., LTD, Shuyang, Chengdu, Sichuan, China).The patient had an mRS score of 4 prior to treatment and improved to a score of 3 post-treatment, though he remained cognitive impairment and mild paresis with muscle strength graded as 4+/5- (medical research council scale) as documented.

Discussion

Among 2,455 citations reviewed for this study, 350 studies were included in a random-effects meta-analysis providing data on 145,721 COVID-19 patients. It is estimated that up to one-third of individuals with

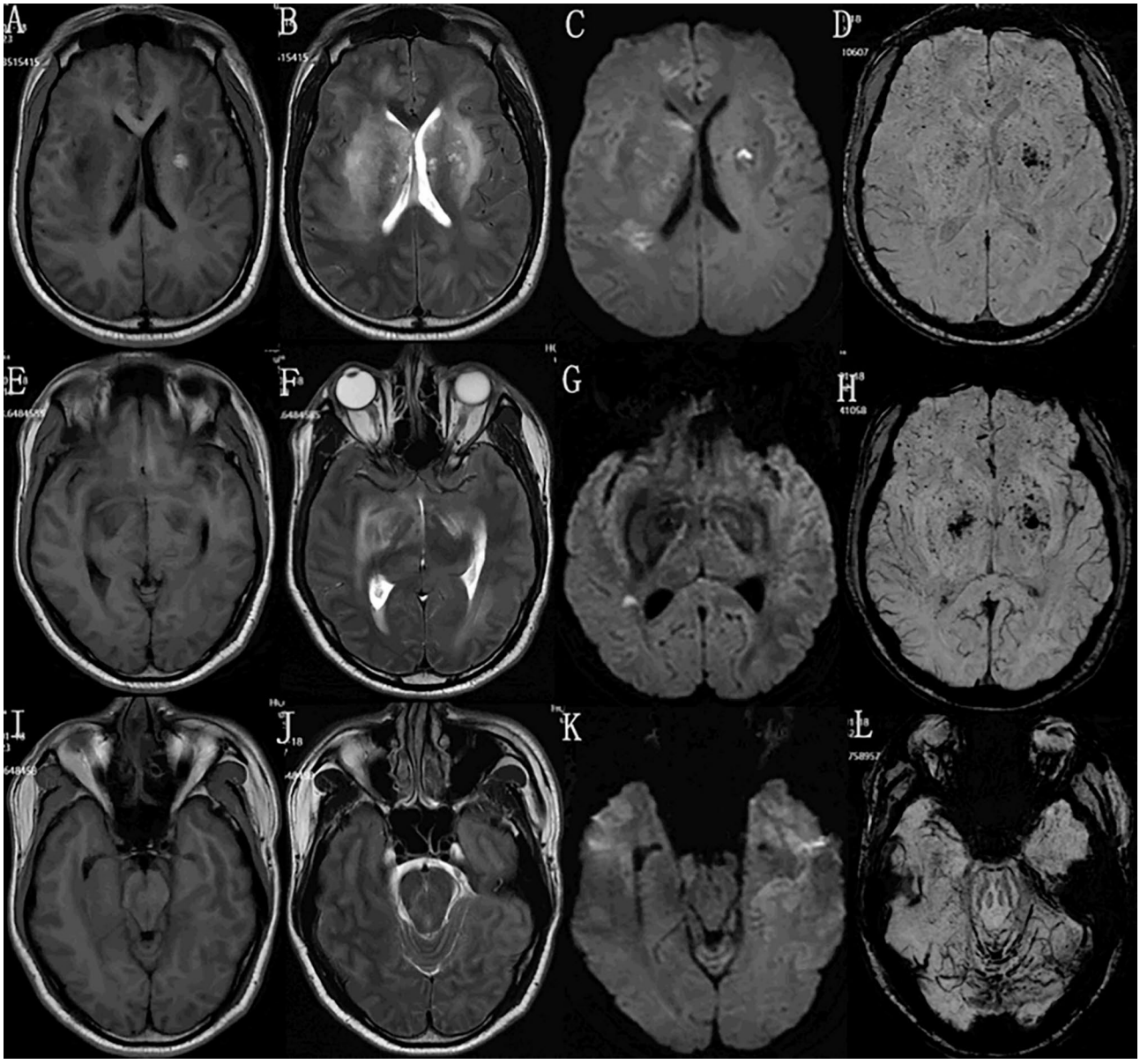

Fig. 3 Patient 3 Encephalitis in a 35-year-old male presenting with fever, seizure and coma. Axial T1-weighted (**A**, **E**, **I**) and T2-weighted (**B**, **F**, **J**) images show abnormal signals in the basal ganglia region, corona radiata, bilateral frontal and temporal regions and pons. Axial diffusion-weighted image (**C**, **G**, **K**) reveals decreased diffusion (high signal intensity) in the same regions. SWI (**D**, **H**, **L**) images reveal dispersed microhaemorrhages in the above lesions that are predominantly located in the basal ganglia and bilateral cerebellar hemispheres

COVID-19 may experience at least one neurological symptom; specifically 2% experiencing a stroke, 7% experiencing encephalopathy and 0.3% experiencing encephalitis. Acute demyelinating, enhemorrhagic or necrotizing ecepahlopathies are often observed in adults with COVID-19 and should be considered when evaluating neuro-COVID patients. MRI appears to be the most effective method for diagnosis, revealing white matter lesions in cases of ADEM, and deep grey matter abnormalities in ANE/AHLE [10].

ANE is not considered to be an inflammatory demyelinating encephalitis, in contrast to ADEM and AHLE. Previous studies have indicated that sporadic ANE is primarily caused by viral infections, particularly influenza and human herpesvirus 6. During the COVID-19 pandemic, several cases of ANE secondary to COVID-19 have been reported. Another type is familial recurrent ANE caused by RANBP2 gene mutations [11]. ANE causes both grey and white matter lesions, which are commonly found in deep grey matter. Symmetric haemorrhage or microhemorrhagic haemorrhage in the brainstem, cerebellar peduncles and thalamus was characteristic, as seen in patients 1 and 2. Blood–brain barrier disruption and dysfunction of vascular endothelial

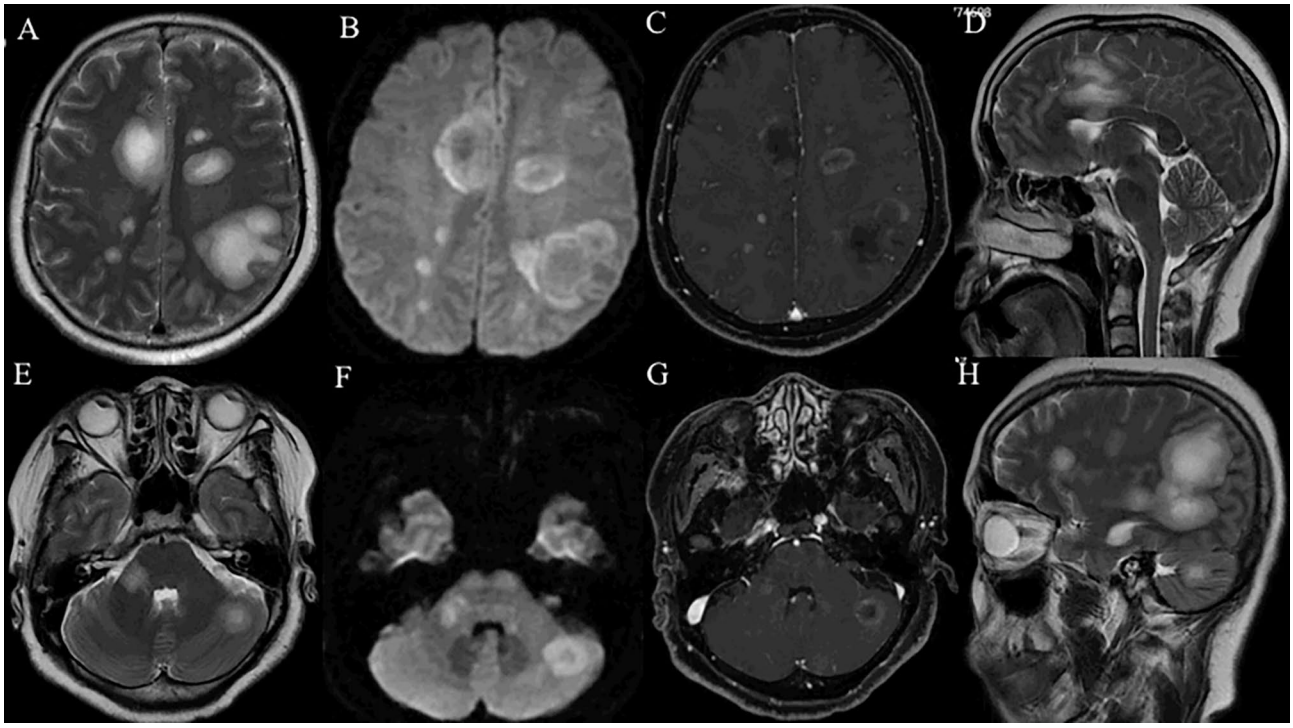

Fig. 4 Patient 4 with acute disseminated encephalomyelitis in a 52-year-old female. Axial T2 (**A** and **E**) and DWI (**B** and **F**) images show multifocal hyperintense lesions, the left cerebellar hemisphere and the right brachium of the pons. Axial postcontrast T1-weighted images (**C** and **G**) reveal mild contrast enhancement of the abnormalities. Sagittal T2-weighted image (**D** and **H**) shows patchy hyperintensity at the frontoparietal temporal lobe

cells may jointly contribute to haemorrhagic pathological changes [12]. Viral infection activates immune-mediated inflammation and can lead to intracranial cytokine storms in ANE disorders [13]. This differs from viral encephalitis, which is mediated by the virus's direct invasion of neuronal intranuclear inclusions, resulting in grey matter damage [14–16]. Most studies have reported increased levels of IL-6 in serum and CSF [17, 18], leading to the use of tocilizumab in patients with severe COVID-19 [19]. However, only the levels of neuroaxonal damage markers 14-3-3 and neurofilament-L (NfL) in CSF significantly correlated with long-term neurologic functional outcome [20]. We did not observe an increase in IL-6 levels among our patients, and the use of tocilizumab did not yield a positive effect for an ANE patient (Patient 1). This finding suggests that not only systemic inflammatory response but also metabolic and mitochondrial dysfunction play a role in the pathological progression of ANE [21]. Our findings are consistent with those of a recent systematic review summarizing the clinical and radiological features of 30 patients with SARS-CoV-2-associated ANE [22]. Bilateral thalamic involvement was identified as the most characteristic MRI finding in that review, frequently extending to the pons and cerebellum—a pattern closely observed in our cohort. The symmetric distribution of T2 FLAIR hyperintense lesions further supports the radiological hallmark of ANE. Although elevated inflammatory markers such as IL-6 were noted in some cases, their lack of specificity for ANE underscores the essential role of neuroimaging in establishing an accurate diagnosis, as well as the generally poor prognosis associated with this condition.

Widespread white matter changes are common features observed in AHLE and ADEM. The imaging patterns of ADEM and AHLE were similar within subcortical white matter with oedema [23]. ADEM most often presents asymmetrically within periventricular regions but with lesser extent involvement within basal ganglia [24]. However, AHLE patients with COVID-19 often exhibit extensive microhemorrhages and gross haemorrhage in the brainstem, cerebellar or cerebral hemisphere [25, 26]. The presence of white matter changes with florid micro- or gross haemorrhage causing a mass effect favouring AHLE and portending a fatal prognosis, as in case 3. Of note, lesional haemorrhage is uncommon in classic demyelinating diseases such as multiple sclerosis [27]. In our patient with AHLE and ADEM, the condition was initiated without prodromic respiratory symptoms. This is different from what has been reported in the previous literature. COVID-19 patients with prodromic respiratory diseases may have indirect brain damage due to hypoxia, sepsis, metabolic changes and other factors [26]. COVID-19-related inflammatory demyelinating encephalopathy or encephalitis without antecedent respiratory

symptoms may develop more rapidly because of a direct attack on the central nervous system by COVID-19, as in patient 3. Perivenous demyelination, lymphocytic infiltration, numerous granulocyte invasions and small perivascular haemorrhages are involved in the progression of AHLE [28]. Fibrin deposition in and around blood vessels was also confirmed in AHLE [29–32]. The pathological manifestation of ADEM is perivenous demyelination with a mild perivascular inflammatory response [30, 33, 34]; hence, intracranial haemorrhage and necrosis are relatively rare. CSF analysis revealed mildly elevated proteins, and emergable lymphocytic pleocytosis supported the diagnosis of inflammatory demyelination but not direct viral invasion or parainfectious demyelination [35] in patients 3 and 4. The difference in mechanism leads to two discrepant outcomes of the two diseases. On the other hand, the neuronal markers NfL and total tau in CSF increased in severe cases of SARS-CoV-2-related encephalitis [36].

Despite the increasing number of reported cases of ADEM and AHLE in patients with SARS-CoV-2 infection, this type of neurological complication remains low considering the total number of infections. A prospective multinational study published in 2023 evaluated 374 adult ICU-treated patients with acute encephalopathy due to severe COVID-19 across six countries. Among them, only one patient was diagnosed with ANE and two with ADEM, highlighting the rare nature of these manifestations despite the global scale of the pandemic [37]. A recent systematic review by Stoijan et al. reported on 74 patients diagnosed with ADEM following either SARS-CoV-2 infection or vaccination, of whom 45 had confirmed post-infectious ADEM and 10 were further classified as having AHLE [38].The median time from infection to onset of neurological symptoms was approximately 19.5 days, ranging from 2 days to 4 months. Notably, most patients had negative CSF PCR results for SARS-CoV-2, reinforcing the hypothesis that these conditions are likely mediated by immune mechanisms rather than direct viral invasion of the central nervous system. This is consistent with our study. Four patients tested positive for SARS-CoV-2 via nucleic acid testing in respiratory tract samples; however, no SARS-CoV-2 was detected in their CSF using mNGS. No significant association was found between the severity of initial COVID-19 illness and clinical outcomes in the post-infection group. However, therapeutic plasma exchange and the presence of coma at presentation were positively correlated with poor outcomes, suggesting that early recognition and intervention may be critical in improving prognosis. The lack of detectable virus in CSF supports a para-infectious or post-infectious immunopathogenic mechanism rather than direct CNS invasion. Similar patterns have been described following other viral infections such as influenza, where CSF test is frequently negative despite a clear clinical association [39].

Acute encephalopathy in patients with COVID-19 may also raise suspicions of posterior reversible encephalopathy syndrome (PRES), Japanese encephalitis (JE), and Wernicke encephalopathy. In PRES, MRI typically reveals symmetrical subcortical signals involving the parieto-occipital lobes, which are reversible in most cases [40]. The difference in lesion location has been utilized to differentiate PRES from ADEM. JE is transmitted by mosquitoes and usually occurs in the summer, predominantly affecting children under 10 years of age [41]. While the thalamus, cerebral cortex, and spinal cord can also be involved in JE, the distribution of lesions is asymmetrical, and the brainstem is rarely affected. With regards to Wernicke encephalopathy, the medial aspects of the thalamus are more commonly involved, aiding in its differentiation from ANE and AHLE [42]. In conclusion, early recognition, investigation and management of COVID-19-related encephalopathy pose a challenge. An imaging presentation showing discrete or bilateral balanced haemorrhage or microhemorrhage should prompt physicians towards a diagnosis of ANE or AHLE necessitating early initiation of appropriate treatment. Based on our findings, acute-onset isolated cognitive or mental impairments should aid in early detection and diagnosis of neuro-coronavirus disease 2019 even without respiratory manifestations.

Our study has limitations, including a small number of cases. This reflects the overall rarity of immune-mediated neurological complications such as ANE and inflammatory demyelinating encephalopathy in the context of SARS-CoV-2 infection. This restricts to drawing definitive conclusion regarding the clinical predictors, optimal treatment strategies, and long-term outcomes associated with these neuroinflammatory manifestations. Larger, multicenter studies are needed to better characterize the epidemiology, pathogenesis, and prognostic factors of neuroinflamatory complications of COVID-19. Secondly, lumbar puncture could not be performed in Patient 2 due to clinical instability, the diagnosis was supported by characteristic MRI findings, confirmed recent SARS-CoV-2 infection, and exclusion of other identifiable etiologies. However, the absence of CSF analysis represents a limitation, as it precluded direct assessment of intrathecal inflammation or the presence of alternative infectious or autoimmune causes.

Conclusion

Early recognition, investigation and management of COVID-19-related encephalopathy is challenging. An imaging picture of discrete, confluent or bilateral balanced haemorrhage or microhemorrhage should prompt the treating physician towards a diagnosis of ANE or

AHLE urging early initiation of adequate treatment. Based on our report, acute-onset and isolated cognitive or mental impairments should assist in the early detection and diagnosis of neuro-coronavirus disease 2019, even in the absence of respiratory manifestations. Despite the small sample size, our study contributes to the comprehensive understanding ANE and ADEM/AHLE linked to SARS-CoV-2 infection by providing detailed insights into their clinical presentation, imaging characteristics, laboratory findings, and treatment responses. These observations, albeit preliminary, lay the groundwork for future studies aiming to uncover the full spectrum and regional variations of post-COVID-19 encephalopathy syndromes.

Abbreviations

ANE	Acute necrotizing encephalopathy
AHLE	Acute hemorrhagic leukoencephalitis
ADEM	Acute disseminated encephalomyelitis
CNS	Central nervous system
IgG	Immunoglobulin G
CSF	Cerebrospinal fluid
RT-PCR	Reverse transcription polymerase chain reaction
MRI	Magnetic resonance imaging
T2W	T2-weighted sequences
T2 FLAIR	T2 fluid-attenuated inversion recovery
SWI	Susceptibility-weighted imaging
DWI	Diffusion-weighted imaging
OCB	Oligoclonal bands
mNGS	Metagenomic next-generation sequencing
AIE	Autoimmune encephalitis
AQP4	Aquaporin-4
MOG	Myelin oligodendrocyte glycoprotein
IL-6	Interleukin-6
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
GCS	Glasgow coma scale
mRS	Modified Rankin Scale
IVMP	Intravenous methylprednisolone succinate
MMSE	Mini-mental state examination
IVIG	Intravenous immunoglobulin
EEG	Electroencephalography
NfL	Neurofilament-L
PRES	Posterior reversible encephalopathy syndrome
JE	Japanese encephalitis
RBCs	Red blood cells in CSF
WBCs	White blood cells in CSF
Pro	Proteins

Supplementary Information

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Supplementary Material 1

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Author contributions
ST wrote the manuscript and was involved in the diagnostic and therapeutic clinical processes. CC contributed to the diagnosis and treatment process and performed data analysis. ES and YS contributed to analyze MR images and figure legends. YC contributed to collect clinical data of patients, conceptualization. WQ and ZL helped in the diagnostic process and critically revising the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval
Written informed consent was obtained from the patient for the participation as well as the publication of the case report and any accompanying images. And this study was approved by the ethics committee of South China Agricultural University (ethical number: CR2023-011-01).A copy of the written consent is available upon request from the corresponding author.

Consent for publication
Written informed consent for publication of identifying images or other personal or clinical details was obtained from the the participants or parents or legal guardians of any participant under the age of 18.

Competing interests
The authors declare no competing interests.

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