Journal of Neurology (2022) 269:2293–2300
https://doi.org/10.1007/s00415-021-10947-2

SHORT COMMENTARY

Encephalopathy as a prognostic factor in adults with acute disseminated encephalomyelitis following COVID-19

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Received: 7 September 2021 / Revised: 22 December 2021 / Accepted: 23 December 2021 / Published online: 3 January 2022

Abstract

Numerous reports support the possible occurrence of acute disseminated encephalomyelitis (ADEM) following COVID-19. Herein, we report a case of ADEM in a 53-year-old man 2 weeks after SARS-CoV-2 infection. We reviewed the reports of adult cases of ADEM and its variant acute necrotizing hemorrhagic leukoencephalitis (ANHLE) to check for possible prognostic factors and clinical/epidemiological peculiarities. We performed a descriptive analysis of clinical and cerebrospinal fluid data. Ordinal logistic regressions were performed to check the effect of clinical variables and treatments on ADEM/ANHLE outcomes. We also compared ADEM and ANHLE patients. We identified a total of 20 ADEM (9 females, median age 53.5 years) and 23 ANHLE (11 females, median age 55 years). Encephalopathy was present in 80% of ADEM and 91.3% of ANHLE patients. We found that the absence of encephalopathy predicts a better clinical outcome in ADEM (OR 0.027, 95% CI 0.001–0.611, $p=0.023$), also when correcting for the other variables (OR 0.032, 95% CI 0.001–0.995, $p=0.05$). Conversely, we identified no significant prognostic factor in ANHLE patients. ANHLE patients showed a trend towards a worse clinical outcome (lower proportion of good/complete recovery, 4.5% vs 16.7%) and higher mortality (36.4% vs 11.1%) as compared to ADEM. Compared to pre-pandemic ADEM, we observed a higher median age of people with post-COVID-19 ADEM and ANHLE, a shorter interval between infection and neurological symptoms, and a worse prognosis both in terms of high morbidity and mortality. Despite being affected by the retrospective nature of the study, these observations provide new insights into ADEM/ANHLE following SARS-CoV-2 infection.

Keywords COVID-19 · ADEM · ANHLE · Acute disseminated encephalomyelitis · Acute necrotizing hemorrhagic leukoencephalitis · Encephalopathy · SARS-CoV-2

Introduction

The ongoing COVID-19 pandemic has extensively shown the multisystemic impact of viral infections. Among the threats posed by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), ample literature supports the possible occurrence of neurological complications [1]. Besides neurovascular diseases, a constantly increasing number of reports regards neuro-inflammatory disorders following COVID-19. Guillan–Barré syndrome, cytotoxic lesion of corpus callosum, acute disseminated encephalomyelitis (ADEM), and its variant acute necrotizing hemorrhagic leukoencephalitis (ANHLE) have all been reported throughout the COVID-19 pandemic [1]. ADEM is an autoimmune demyelinating disease of the central nervous system (CNS), preferentially occurring in childhood, but affecting also adults [2]. It is typically characterized by an acute, monophasic course with multifocal neurological signs and symptoms. While encephalopathy is a required feature for ADEM diagnosis in children, in adults it has been reported in only 20–56% of cases [3–5]. In adults, ADEM is associated with a previous infection in 50–75% of cases, with a lag period ranging from [4–6] few days to 2 months. Concerning prognosis, a complete recovery has been reported in 10–46% of the adult patients [3, 5, 7] with mortality ranging from 4 to 12% [3, 5, 8].

We recently faced the challenge of diagnosing and managing ADEM occurred in the context of COVID-19 disease. Herein, we report the case of a 53-year-old man

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who developed ADEM following SARS-CoV-2 infection. Furthermore, we reviewed the current literature concerning ADEM and ANHLE adult cases likely triggered by SARS-CoV-2, checking for possible prognostic factors and differences between ADEM and ANHLE.

Case report

A 53-year-old male patient developed a febrile episode with mild respiratory symptoms. A nasal swab tested positive for SARS-CoV-2 RNA. Two weeks later, he presented with subacute bilateral blindness. He was admitted to a COVID-19 department of our hospital, since a nasal swab was still positive for SARS-CoV-2 RNA. The patient deserved non-invasive oxygen therapy because of mild hypoxia. Head CT showed a mild hypodensity in the right occipital lobe, while a CT-angiography was unrevealing. In the following days, the patient developed a subacute encephalopathy characterized by fluctuations in consciousness level, spatial and temporal disorientation associated with severe dysarthria, ophthalmoplegia, left hemiparesis, four limbs ataxia, and left upper limb dystonia associated with facial and left arm stereotypic movement disorder. Brain MRI showed the presence of supra- and infratentorial bilateral hyperintense white matter lesions (Fig. 1A–D), with incomplete gadolinium enhancement (Fig. 1F–I). Spinal cord MRI revealed a dorsal enhancing lesion (Fig. 1E, J). A lumbar puncture was performed. CSF analysis showed 1 cell/μl with a mild increase in protein concentration (74 mg/dl). Oligoclonal bands (OCB) were negative. PCR performed on CSF were negative for neurotropic viruses (VZV, HSV 1–2, EBV, CMV, enterovirus), including SARS-CoV-2. Anti-MOG anti-AQP4 both tested negatives. Anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-CV2, anti-Ma proteins, anti-amphiphysin, and anti-GAD also tested negative. According to the clinical picture and the radiological findings, along with the unrevealing CSF analysis, the patient was diagnosed with ADEM. High-dose intravenous methylprednisolone was administered (1 g for 7 days followed by intravenous tapering for a total of 10.5 g), together with intravenous immunoglobulins (IVIG) (2 g/kg in 5 days), obtaining a stabilization of the neurological picture followed by a mild recovery. The clinical course was complicated by recurrent infections (C. Albicans and E. faecium sepsis, K. Pneumonia urinary infection) and by spontaneous retroperitoneal hemorrhage. A follow-up MRI performed 1 month later documented a stable lesion load, with a persistent enhancement of part of the lesions. 5-day IVIG therapy was then again administered. Three weeks later, a follow-up MRI showed a significant reduction of gadolinium enhancement. Further 3 days of IVMP were administered. At the moment of the present report, the patient only recovered partially, with neurological examination showing bilateral blindness, partial time and space disorientation, moderate dysarthria, echolalia, four limbs and truncal ataxia with an inability to walk.

The patient and his wife provided informed consent for this report.

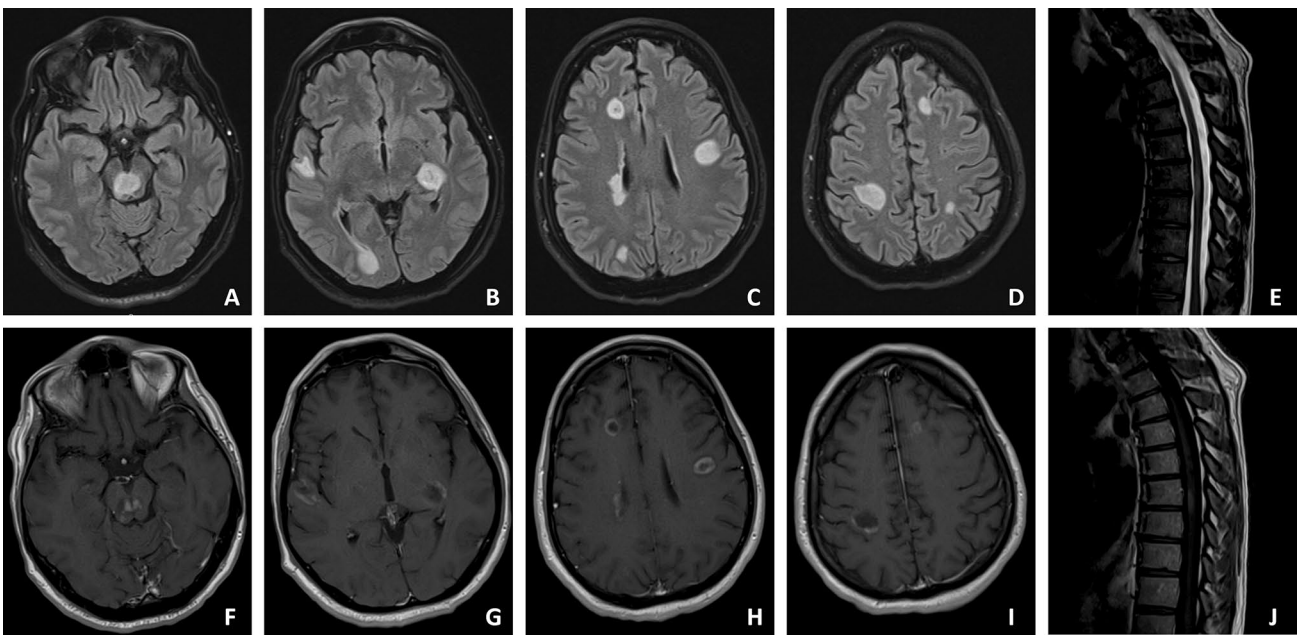

Fig. 1 Brain and spinal cord MRI. Brain MRI showing supra- and infratentorial bilateral FLAIR-hyperintense white matter lesions suggestive of ADEM (A–D). In (E) spinal cord MRI documenting a T2-hyperintense dorsal lesion. After gadolinium administration, brain (F–I) and spinal cord (J) are characterized by incomplete contrast enhancement

Review

Methods

We performed a literature review, searching on PubMed the papers concerning the occurrence of ADEM or ANHLE in patients with SARS-CoV-2 infection, published in the English language from the beginning of the pandemic to early June 2021. Concerning ANHLE, all the studies describing "acute necrotizing hemorrhagic leukoencephalitis", "acute necrotizing encephalopathy", and "acute hemorrhagic encephalomyelitis" and "acute hemorrhagic leukoencephalitis" were considered. We used the following search strategy: [ADEM OR acute disseminated encephalomyelitis OR acute necrotizing hemorrhagic leukoencephalitis OR ANHLE OR acute necrotizing encephalopathy OR ANE OR acute hemorrhagic encephalomyelitis OR AHEM OR acute hemorrhagic leukoencephalitis OR AHLE OR acute necrotizing leukoencephalitis OR ANLE] AND [COVID-19 OR SARS-CoV-2 OR COVID OR coronavirus disease]. The search identified 254 papers. Article titles and abstracts were screened by the authors of the present paper, including all the works potentially relevant for the search topic. Among the 254 papers screened, 48 were identified as relevant and underwent a full-text assessment to check eligibility according to the inclusion criteria of the present review. First, as previously published by other authors, we included patients whose case descriptions provided clinical and radiological details sufficient for ADEM or ANHLE diagnosis [9]. ADEM was defined as the acute onset of multifocal neurological signs/symptoms supported by white matter lesions suggestive of demyelination at central nervous system MRI [9]. ANHLE was defined by the evidence of micro- and/or macro-hemorrhage at brain MRI along with a hyperacute onset of the disease [9]. The studies were then selected according to the following inclusion criteria: adult patients (i.e., $\geq$ 18 years); SARS-CoV-2 infection confirmed with RT-PCR or serum antibody test; availability of clinical and radiological data; fulfillment of criteria for a probable association between SARS-CoV-2 infection and ADEM/ANHLE (neurological symptoms within 6 weeks from SARS-CoV-2 infection; either a PCR test positive for SARS-CoV-2 RNA or serology suggestive for SARS-CoV-2 acute infections; no evidence of other causes) [1]. Studies describing pathological or MRI findings without a clinical picture suggestive of ADEM or ANHLE were not included in the analyses. Following the application of the inclusion criteria, we retained 32 papers (14 concerning ADEM, 18 ANHLE) reporting a total of 43 cases (20 ADEM, 23 ANHLE) (Fig. 2).

We classified the patients according to the severity of COVID-19 infection and the clinical outcome of the neurological disease. COVID-19 severity was classified, adapting previous classification [10] into: asymptomatic, mild, severe, and critical. Asymptomatic were patients with no respiratory symptoms. Mild disease included patients without pneumonia or with mild pneumonia; patients with dyspnea and hypoxia who required oxygen therapy were defined as severe; critical disease was defined by the need for mechanical ventilation and/or the occurrence of shock and/or multiorgan failure. The clinical outcome of the neurological disease was categorized as follows: complete recovery, good recovery, partial/poor recovery, no recovery, death. Complete recovery was defined by a normal neurological examination at follow-up; good recovery by the persistence of mild neurological signs/symptoms, likely not affecting the activity of daily living; partial/poor recovery was defined by the persistence of significant neurological disability; no recovery when the neurological picture did not improve over time.

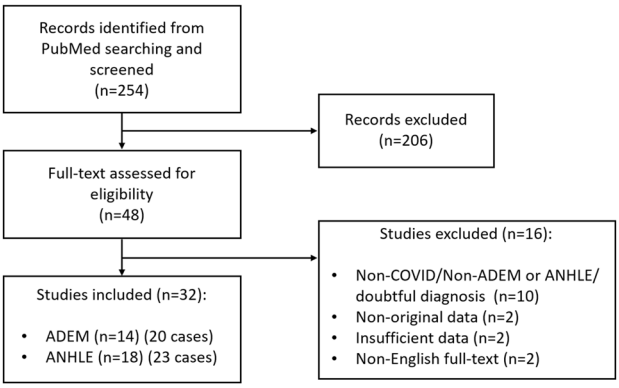

Fig. 2 Search strategy flow chart

Analyses were performed with SPSS statistical 26.0 (IBM SPSS, NY, USA). Univariate and multivariate ordinal logistic regressions were performed to check the effect of different variables on the clinical outcome of ADEM and ANHLE patients.

Results

ADEM

According to the inclusion criteria, we identified 14 studies reporting a total of 20 patients who developed ADEM following SARS-CoV-2 infection [10–23]. The infection was confirmed by a nasal swab positive for SARS-CoV-2 RNA (RT-PCR) in all but one patient [22]. In this case, the infection was documented with a positive SARS-CoV-2 serology [22].

Patients with ADEM had a median age of 53.5 years (range 21–70, IQR 40–58.25) with males accounting for the

55% of the total (Table 1). In 15% of patients, the SARS-CoV-2 infection was asymptomatic, while mild symptoms were observed in 25%. The 60% of patients developing ADEM had a critical course of COVID-19 infection. The main reason requiring hospitalization was neurological for the 40% of patients, while the remaining were hospitalized because of the respiratory clinical course. The median time between SARS-CoV-2 documented infection and the development of neurological symptoms was 15.5 days (IQR 9.5–20.5 days). Encephalopathy was present in 80% of the patients. In 50% of the cases, a neurological disorder was suspected following consciousness impairment despite withdrawal from sedation. Spinal cord MRI was performed in 10 out of 20 patients, revealing an incidence of spinal cord demyelinating lesions of 70%. Cerebrospinal fluid (CSF) was collected in 19 patients. In 17 of those, oligoclonal bands (OCB) were measured, obtaining only two positive results (11.8%). The median number of CSF nucleated cells was 3/µl (IQR 1.25–6/µl) and median CSF proteins were 48.85 mg/dl (IQR 35.25–57.5 mg/dl). CSF PCR analysis for SARS-CoV-2 was reported in 15 cases, with only two positive results [12, 14] (one of those was uncertain [14]). Anti-MOG and anti-AQP4 antibodies were, respectively, tested in 5 and 6 patients with all negative results. The treatment approach was reported in 18 cases, varying among the different reports. In two cases (11.1%) no specific treatment was administered [10, 18]. Three patients (16.7%) were treated with low dosage steroid therapy [19, 20, 23]. In four cases (22.2%), high dose IVMP pulse therapy was administered followed by steroid oral tapering [10, 11]. In five patients (27.8%), IVMP was followed by the administration of intravenous immunoglobulin (IVIG) [12–14, 20]. One patient received IVIG alone [15] and another one was treated with 5-day plasmapheresis (PLEX) [22]. Finally, two patients were treated with rituximab (11.1%), one following IVMP [17] and the other following IVMP and PLEX treatment [21]. The clinical outcome was reported in 18 cases. One patient showed complete recovery from the neurological

Table 1 Clinical and CSF data of ADEM and ANHLE patients

	ADEM	ANHLE
Number of patients (*n*)	20	23
Female (%)	45%	47.8%
Age (years)	53.5 ± 40–58.25	55 ± 46.75–58.25
Severity of COVID-19 infection (%)		
Asymptomatic	15%	0%
Mild	25%	34.8%
Severe	0%	8.7%
Critical	60%	56.5%
Main reason for hospitalization: neurological	40%	52.2%
Lag time between infection and neurological disease (days)	15.5 ± 9.5–20.5	9 ± 2–5–20.75
Presence of encephalopathy	80%	91.3%
Presenting with difficult awakening from sedation	50%	30.4%
Presence of spinal cord lesion	70% (*n* = 10)	*Na*
CSF		
OCB presence	11.8% (*n* = 17)	33.3% (*n* = 3)
Cells/ML	3 ± 1.25–6 (*n* = 19)	4 ± 3–5 (*n* = 18)
Protein (mg/dl)	48.85 ± 35.25–57.5 (*n* = 19)	230 ± 80–5–605.5 (*n* = 18)
Anti-MOG	0% (*n* = 5)	0% (*n* = 1)
Anti-AQP4	0% (*n* = 6)	0% (*n* = 1)
Neurological clinical outcome:	*n* = 18	*n* = 22
Complete recovery	5.6%	0%
Good recovery	11.1%	4.5%
Partial/poor recovery	55.6%	59.1%
No recovery	16.7%	0%
Death	11.1%	36.4%

Data are expressed as percentage or median ± interquartile range. Sample size of the analyses are specified in brackets when the specific variable was not available for all the reported patients.

ADEM acute disseminated encephalomyelitis, *ANHLE* acute necrotizing hemorrhagic leukoencephalitis, *CSF* cerebrospinal fluid, *na* not applicable, *OCB* oligoclonal bands

symptoms and signs (5.6%) [10]. A good clinical recovery was observed in two patients (11.1%) [12, 17], while partial/poor recovery was observed in ten (55.6%) [10, 11, 13, 14, 18, 20, 22] and no recovery in three patients (16.7%) [15, 20, 21]. Two patients died (11.1%) [18, 19].

Univariate ordinal logistic regressions were performed to check the effect of age, sex, the severity of COVID-19 symptoms, main reason for hospitalization (respiratory vs neurological), the presence of encephalopathy, OCB status, the presence of spinal cord lesions, and the treatment on the clinical outcome of patients with ADEM. We found that the absence of encephalopathy was associated with a lower risk of a worse clinical outcome, OR 0.027 (95% CI 0.001–0.611), Wald χ^2 (1) = 5.153, $p = 0.023$. On the opposite, no effect was observed for the other variables. We then performed a multivariate ordinal logistic regression including encephalopathy, the reason for hospitalization, and the COVID-19 severity. In this model, the absence of encephalopathy was the only significant predictor of clinical outcome (OR 0.032 (95% CI 0.001–0.995), Wald χ^2 (1) = 3.854, $p = 0.05$).

ANHLE

According to the inclusion criteria we identified in the literature 18 studies reporting the occurrence of ANHLE in 23 patients following SARS-CoV-2 infection [10, 24–40]. The infection was confirmed with a nasal swab positive for SARS-CoV-2 RNA (RT-PCR) in all but one patient [10].

The median age of patients with ANHLE was 55 years (range 33–77, IQR 46.75–58.25) with males representing 52.2% of the patients (Table 1). In all the reported cases. The SARS-CoV-2 infection was symptomatic. 34.8% of patients had mild symptoms, while a severe course was observed in 8.7% and critical disease in 56.5%. The main reason for hospitalization was neurological in 52.2% of the patients. The median time between SARS-CoV-2 infection and the onset of neurological symptoms was 9 days (IQR 2–5–20.75 days). 91.3% of the patients presented with encephalopathy. An altered consciousness state after the end of sedation arose the suspicion of a CNS neurological disorder in 30.4% of the cases [10, 24, 28, 30, 39]. In one case ANHLE was associated with AIDP [10]. CSF was collected in 18 patients. OCB were measured in three patients with one positive result [28]. The median number of CSF nucleated cells was 4/µl (IQR 3–5/µl), and median CSF protein concentration was 230 mg/dl (IQR 80–5–605.5 mg/dl). CSF PCR analysis for SARS-CoV-2 was reported in 13 cases with one positive result [25]. Anti-MOG and anti-AQP4 antibodies were tested in one patient with negative results [27]. The treatment strategy was reported in all cases. Six patients (26.1%) received no specific treatment [10, 28, 30, 35, 38, 39]. Three patients (13%) received low-dose steroid treatment [10, 30, 31]. Six patients (26.1%) were treated with IVMP pulse therapy [10, 32, 33, 36, 37, 40] and six others (26.1%) with IVMP followed by IVIG [10, 24, 26, 27, 34]. One patient was treated with IVIG and PLEX [25], another with IVIG alone [29]. The clinical outcome was reported for 22 patients. No patient showed a complete recovery. Good clinical recovery was observed in one patient (4.5%) [39], while partial/poor recovery was reported in 13 cases (59.1%) [10, 24–26, 28, 33–35, 38, 40]. Eight patients died (36.4%) [10, 27, 30–32, 36, 37]. In one case the diagnosis was pathologically confirmed [10].

Univariate ordinal logistic regressions were performed to check the effect of age, sex, the severity of COVID-19 symptoms, main reason for hospitalization (respiratory vs neurological), the presence of encephalopathy, and the treatment on the clinical outcome of patients with ANHLE. We found that female patients have an increased risk for a worse outcome, OR 8.035 (95% CI 1.132–57.132), Wald χ^2 (1) = 4.343, $p = 0.037$. No effect was observed for the other tested variables. The effect of gender on the clinical outcome, however, did not survive to a multivariate ordinal logistic regression including the main reason for hospitalization and sex ($p = 0.095$).

ADEM vs ANHLE

We then compared ADEM and ANHLE patients to check for any possible differences in clinical and CSF characteristics. Mann–Whitney showed no difference concerning age, the time between SARS-CoV-2 infection and neurological disease, CSF nucleated cells. We run Chi-square test of homogeneity with no differences between groups in terms of gender, the incidence of encephalopathy, the main reason for hospitalization, COVID-19 disease severity. We found a trend toward significance for the clinical outcome ($p = 0.091$), with ANHLE group having a higher incidence of fatal course (36.4% vs 11.1%) and a lower proportion of good or complete recovery (4.5% vs 16.7%).

Discussion

Our report confirms the possible occurrence of ADEM following SARS-CoV-2 infections in adult patients. We reviewed the literature available at the moment of the present report, addressing clinical and CSF findings. We also checked for possible prognostic factors, comparing ADEM and ANHLE patients.

Previous studies have reviewed the cases of ADEM [9, 41, 42] and ANHLE9 following COVID-19. However, those studies did not focus on possible disease prognostic factors nor the clinical differences between ADEM and ANHLE. Clinical [43] and radiological [43, 44] prognostic

factors have been previously proposed for the risk of multiphasic ADEM, both for children and adult pre-pandemic patients [43, 44]. Conversely, to date, no factor predicting the outcome of the disease was identified. In the present study, we observed that the absence of encephalopathy was associated with a lower risk of a worse clinical outcome in ADEM patients, both in univariate and multivariate analyses. On the opposite, we failed to identified valuable prognostic factors for ANHLE patients. We found that encephalopathy was present in 80% of ADEM and 91.3% of ANHLE patients. This incidence appears to be higher as compared to what was previously reported in pre-pandemic ADEM patients (20–56%) [3–5]. Furthermore, in 50% of ADEM patients and 30.4% of ANHLE patients, difficult awakening from sedation was the presenting neurological symptoms, suggesting the need to promptly investigate encephalopathy in COVID-19 patients.

Despite the growing number of ADEM and ANHLE reports in people with SARS-CoV-2 infection, the development of these neurological complications is very rare. At the time of the present report, the global number of SARS-CoV-2 infections counted from the beginning of the pandemic exceeded 175 million (WHO COVID-19 weekly epidemiological update, edition 44, published 15 June 2021, available at https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---15-june-2021). Against the ample number of SARS-CoV-2 infections, we identified only 43 reported patients who developed ADEM or ANHLE in the context of COVID-19, with a prevalence of about 2.4 cases per 10,000,000 COVID-19 patients. This prevalence is much lower than what is expected in the general population. In a previous study published before the pandemic, the prevalence of ADEM was 3.3 per 100,000 population [45]. This 100-fold difference may be at least partially explained by an under-reporting of ADEM/ANHLE cases in COVID-19. Conversely, one could argue that SARS-CoV-2 may be a less effective trigger for ADEM, as compared to other viral infections. While the prevalence of ANHLE is not established, it is usually considered a rare variant of ADEM [46]. Interestingly, we identified a higher number of ANHLE reports as compared to ADEM. As previously highlighted by Manzano et al., other significant epidemiological differences exist between pre-pandemic ADEM and post-COVID-19 ADEM [9]. We observed a higher median age of people with ADEM (55 years vs 33–41 years [3, 5, 44, 47, 48]) and ANHLE (55 years vs 38 years [46]), a shorter lag time between infection and neurological symptoms [47] and a worse prognosis both in terms of high morbidity and mortality [3, 5, 7, 8] and the absence of anti-MOG antibodies in ADEM patients. When comparing ADEM and ANHLE, we observed a higher mortality and worse prognosis trend in ANHLE patients, consistently with previous studies [46].

Our findings should be read in light of the study limitations. These include the small sample size, and the retrospective collection of published reports, which are highly variable in terms of data reporting and quality. Moreover, our analyses concerning prognosis were based on a retrospective categorization of clinical outcomes that may have biased the study. In addition, follow-up periods were mostly short and not clearly specified in most of the studies, being another possible source of bias. Other study limitations are the low number of anti-MOG and anti-AQP testing and the possible under-reporting of ADEM/ANHLE cases.

Despite these limitations, the present study, suggests encephalopathy as a possible prognostic factor in post-COVID-19 ADEM and highlights the possible epidemiological differences between pre-pandemic and post-COVID-19 ADEM in adults. Future prospective multi-center studies are needed to shed light on this rare but yet possible complication of SARS-CoV-2 infection.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declarations

Conflicts of interest The authors declare no conflicting interests concerning the present study.

Informed consent The patient and his wife provided informed consent for this report.

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