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

Stefano Gelibter (s.gelibter@gmail.com)
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia https://orcid.org/0000-0001-7388-4124
Gabriele Bellavia
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia
Carla Arbasino
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia
Natale Arnò
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia
Margaret Glorioso
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia
Sara Mazza
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia
Rosanna Murelli
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia
Massimo Sciarretta
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia
Carlo Dallocchio
ASST di Pavia: Azienda Socio Sanitaria Territoriale di Pavia

Research Article

Keywords: COVID-19, ADEM, ANHLE, acute disseminated encephalomyelitis, acute necrotizing hemorrhagic leukoencephalitis, encephalopathy, SARS-CoV-2

Posted Date: October 5th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-887882/v1

Version of Record: A version of this preprint was published at Journal of Neurology on January 3rd, 2022. See the published version at https://doi.org/10.1007/s00415-021-10947-2.

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 years-old man two 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.

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 two 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-years-old man 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 years 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, including SARS-CoV-2. Anti-MOG anti-AQP4 both tested negatives. 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 gram for 7 days followed by intravenous tapering for a total of 10.5 grams), together with intravenous immunoglobulins (IVIG) (2 grams/kg in five 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 one month later documented a stable lesion load, with a persistent enhancement of part of the lesions. 5 days 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.

Review

Methods

We performed a literature review, searching on PubMed and Google Scholar 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” were considered. The studies were then selected according to the following inclusion criteria: adult patients (i.e., ≥ 18 years); SARS-CoV-2 infection confirmed with RT-PCR or serum antibody test; availability of clinical and radiological data; clinical and radiological findings compatible with an ADEM or ANHLE diagnosis; fulfillment of criteria for a probable association between SARS-CoV-2 infection and ADEM[1]. Studies describing pathological or MRI findings without a clinical picture suggestive of ADEM or ANHLE were not included in the analyses.

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 [9] 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.

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 [9–22].

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. 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[11,13] (one of those was uncertain [13]). 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 [9,17]. Three patients (16.7%) were treated with low dosage steroid therapy [18,19,22]. In four cases (22.2%), high dose IVMP pulse therapy was administered followed by steroid oral tapering [9,10]. In five patients (27.8%), IVMP was followed by the administration of intravenous immunoglobulin (IVIG) [11–13, 19]. One patient received IVIG alone [14] and another one was treated with 5-days plasmapheresis (PLEX) [21]. Finally, two patients were treated with rituximab (11.1%), one following IVMP [16] and the other following IVMP and PLEX treatment [20]. The clinical outcome was reported in 18 cases. One patient showed complete recovery from the neurological symptoms and signs (5.6%) [9]. A good clinical recovery was observed in two patients (11.1%) [11,16], while partial/poor recovery was observed in ten (55.6%) [9,10,12,13,17,19,21] and no recovery in three patients (16.7%) [14,19,20]. Two patients died (11.1%) [17,18].

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 $\chi 2$ (1) = 5.153, p = 0.023. We also found a trend towards a significant effect of the reason for hospitalization (neurological vs respiratory) (p = 0.065) and the severity of COVID-19 symptoms (p = 0.13). 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 $\chi 2$ (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 [9,23–39].

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. 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 [9,23,27,29,38]. In one case ANHLE was associated with AIDP[9]. CSF was collected in 18 patients. OCB were measured in three patients with one positive result [27]. 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 [24]. Anti-MOG and anti-AQP4 antibodies were tested in one patient with negative results [26]. The treatment strategy was reported in all cases. Six patients (26.1%) received no specific treatment [9,27,29,34,37,38]. Three patients (13%) received low-dose steroid treatment [9,29,30]. Six patients (26.1%) were treated with IVMP pulse therapy[9,31,32,35,36,39] and six others (26.1%) with IVMP followed by IVIG[9,23,25,26,33]. One patient was treated with IVIG and PLEX [24], another with IVIG alone[28]. The clinical outcome was reported for 22 patients. No patient showed a complete recovery. Good clinical recovery was observed in one patient (4.5%) [38], while partial/poor recovery was reported in 13 cases (59.1%) [9, 23–25,27, 32–34,37,39]. Eight patients died (36.4%) [9,26, 29–31,35,36]. In one case the diagnosis was pathologically confirmed [9].

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 $\chi 2$ (1) = 4.343, p = 0.037. We also found a trend towards a significant effect of the reason for hospitalization (neurological vs respiratory) (p = 0.067). 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 observed a trend towards significance in protein concentration (p = 0.087). We a 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 [40–42] and ANHLE[40] 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 ADEM (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 [40]. 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.

Table 1

– Clinical and CSF data of ADEM and ANHLE patients – 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. Abbreviations: ADEM = acute disseminated encephalomyelitis, ANHLE = acute necrotizing hemorrhagic leukoencephalitis, CSF = cerebrospinal fluid, *na* = not applicable, OCB = oligoclonal bands.

	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/µl	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%

	ADEM	ANHLE
no recovery	16.7%	0%
Death	11.1%	36.4%

Declarations

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

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

Declaration of conflicting interests: The authors declare no conflicting interests concerning the present study.

References

1. Ellul MA, Benjamin L, Singh B et al (2020) Neurological associations of COVID-19. Lancet Neurol 19(9):767–783
2. Pohl D, Alper G, Van Haren K et al (2016) Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. Neurology 87(9 Supplement 2):S38–S45
3. Schwarz S, Mohr A, Knauth M et al (2001) Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. Neurology 56(10):1313–1318
4. Koelman DLH, Chahin S, Mar SS et al (2016) Acute disseminated encephalomyelitis in 228 patients: A retrospective, multicenter US study. Neurology 86(22):2085–2093
5. Ketelslegers IA, Visser IER, Neuteboom RF et al (2011) Disease course and outcome of acute disseminated encephalomyelitis is more severe in adults than in children. Mult Scler 17(4):441–448
6. Noorbakhsh F, Johnson RT, Emery D, Power C (2008) Acute disseminated encephalomyelitis: clinical and pathogenesis features. Neurol Clin 26(3):759–780, ix
7. Höllinger P, Sturzenegger M, Mathis J et al (2002) Acute disseminated encephalomyelitis in adults: a reappraisal of clinical, CSF, EEG, and MRI findings. J Neurol 249(3):320–329
8. Marchioni E, Marinou-Aktipi K, Uggetti C et al (2002) Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis. J Neurol 249(1):100–104
9. Paterson RW, Brown RL, Benjamin L et al (2020) The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 143(10):3104–3120
10. Langley L, Zeicu C, Whitton L, Pauls M (2020) Acute disseminated encephalomyelitis (ADEM) associated with COVID-19. BMJ Case Rep 13(12):e239597

11. Novi G, Rossi T, Pedemonte E et al (2020) Acute disseminated encephalomyelitis after SARS-CoV-2 infection. Neurol Neuroimmunol Neuroinflamm 7(5):e797
12. Parsons T, Banks S, Bae C et al (2020) COVID-19-associated acute disseminated encephalomyelitis (ADEM). J Neurol 267(10):2799–2802
13. Utukuri PS, Bautista A, Lignelli A, Moonis G. Possible Acute Disseminated Encephalomyelitis Related to Severe Acute Respiratory Syndrome Coronavirus 2 Infection. AJNR Am J Neuroradiol 2020;ajnr;ajnr.A6714v1
14. Umapathi T, Quek WMJ, Yen JM et al. Encephalopathy in COVID-19 patients; viral, parainfectious, or both? eNeurologicalSci 2020;21:100275
15. Assunção FB, Fragoso DC, Donoso Scoppetta TLP, Martins Maia AC (2021) COVID-19-Associated Acute Disseminated Encephalomyelitis–Like Disease. AJNR Am J Neuroradiol 42(4):E21–E23
16. Shahmirzaei S, Naser Moghadasi A (2021) Association of COVID-19 and Acute Disseminated Encephalomyelitis (ADEM) in the absence of pulmonary involvement. Autoimmun Rev 20(3):102753
17. Lopes CCB, Brucki SMD, Passos Neto CEB et al (2020) Acute Disseminated Encephalomyelitis in COVID-19: presentation of two cases and review of the literature. Arq Neuro-Psiquiatr 78(12):805–810
18. Abdi S, Ghorbani A, Fatehi F (2020) The association of SARS-CoV-2 infection and acute disseminated encephalomyelitis without prominent clinical pulmonary symptoms. J Neurol Sci 416:117001
19. McCuddy M, Kelkar P, Zhao Y, Wicklund D (2020) Acute Demyelinating Encephalomyelitis (ADEM) in COVID-19 Infection: A Case Series. Neurol India 68(5):1192–1195
20. Fitouchi S, Heger B, Kremer L et al. A case of acute disseminate encephalomyelitis after SARS-CoV-2 related acute respiratory distress syndrome. J Neuroradiol 2020
21. Zoghi A, Ramezani M, Roozbeh M et al (2020) A case of possible atypical demyelinating event of the central nervous system following COVID-19. Multiple Sclerosis Related Disorders 44:102324
22. Brun G, Hak J-F, Coze S et al (2020) COVID-19—White matter and globus pallidum lesions: Demyelination or small-vessel vasculitis? Neurol Neuroimmunol Neuroinflamm 7(4):e777
23. Yong MH, Chan YFZ, Liu J et al (2020) A Rare Case of Acute Hemorrhagic Leukoencephalitis in a COVID-19 Patient. J Neurol Sci 416:117035
24. Virhammar J, Kumlien E, Fällmar D et al (2020) Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. Neurology 95(10):445–449
25. Delamarre L, Gollion C, Grouteau G et al (2020) COVID-19–associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. J Neurol Neurosurg Psychiatry 91(9):1004–1006
26. Ghosh R, Dubey S, Finsterer J et al. SARS-CoV-2-Associated Acute Hemorrhagic, Necrotizing Encephalitis (AHNE) Presenting with Cognitive Impairment in a 44-Year-Old Woman without

Comorbidities: A Case Report [Internet]. Am J Case Rep 2020;21[cited 2021 Jun 19] Available from: https://www.amjcaserep.com/abstract/index/idArt/925641

27. Haqiqi A, Samuels TL, Lamb FJ et al Acute haemorrhagic leukoencephalitis (Hurst disease) in severe COVID- 19 infection. Brain, Behavior, & Immunity - Health 2021;12:100208
28. Poyiadji N, Shahin G, Noujaim D et al (2020) COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. Radiology 296(2):E119–E120
29. Mullaguri N, Sivakumar S, Battineni A et al. COVID-19 Related Acute Hemorrhagic Necrotizing Encephalitis: A Report of Two Cases and Literature Review [Internet]. Cureus 2021;[cited 2021 Jun 27] Available from: https://www.cureus.com/articles/50440-covid-19-related-acute-hemorrhagic-necrotizing-encephalitis-a-report-of-two-cases-and-literature-review
30. Dixon L, Varley J, Gontsarova A et al (2020) COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. Neurol Neuroimmunol Neuroinflamm 7(5):e789
31. Elkady A, Rabinstein AA (2020) Acute necrotizing encephalopathy and myocarditis in a young patient with COVID-19. Neurol Neuroimmunol Neuroinflamm 7(5):e801
32. Ciolac D, Crivorucica I, Zota E et al (2021) Extensive cerebellar involvement and cognitive impairment in COVID-19-associated acute necrotizing encephalopathy. Ther Adv Neurol Disord 14:175628642098517
33. Bansal P, Fory EK, Malik S, Memon AB (2020) Clinical Course of a Patient with Radiographically Described Acute Necrotizing Encephalopathy. Radiology 297(2):E278–E280
34. Krett JD, Jewett GAE, Elton-Lacasse C et al (2020) Hemorrhagic encephalopathy associated with COVID-19. J Neuroimmunol 346:577326
35. Varadan B, Shankar A, Rajakumar A et al (2021) Acute hemorrhagic leukoencephalitis in a COVID-19 patient—a case report with literature review. Neuroradiology 63(5):653–661
36. Handa R, Nanda S, Prasad A et al (2020) Covid-19-associated acute haemorrhagic leukoencephalomyelitis. Neurol Sci 41(11):3023–3026
37. Chalil A, Baker CS, Johnston RB et al (2021) Acute Hemorrhagic Encephalitis Related to COVID-19. Neurol Clin Pract 11(2):e147–e151
38. Karapanayiotides T, Geka E, Prassopoulos P et al. Concentric demyelination pattern in COVID-19-associated acute haemorrhagic leukoencephalitis: a lurking catastrophe? Brain 2020;143(12):e100–e100
39. Green C, Morrison H, Smith P et al. Teaching Neuroimages: COVID-19 associated acute disseminated encephalomyelitis with corpus callosal hemorrhage. Neurology 2020;10.1212/WNL.0000000000011001
40. Manzano GS, McEntire CRS, Martinez-Lage M et al (2021) Acute Disseminated Encephalomyelitis and Acute Hemorrhagic Leukoencephalitis Following COVID-19: Systematic Review and Meta-synthesis. Neurol Neuroimmunol Neuroinflamm 8(6):e1080

41. Zelada-Ríos L, Pacheco-Barrios K, Galecio-Castillo M et al (2021) Acute disseminated encephalomyelitis and COVID-19: A systematic synthesis of worldwide cases. J Neuroimmunol 359:577674
42. Wang Y, Wang Y, Huo L et al. SARS-CoV-2-associated acute disseminated encephalomyelitis: a systematic review of the literature [Internet]. J Neurol 2021;[cited 2021 Sep 3] Available from: https://link.springer.com/10.1007/s00415-021-10771-8
43. Mikaeloff Y, Caridade G, Husson B et al (2007) Acute disseminated encephalomyelitis cohort study: Prognostic factors for relapse. European Journal of Paediatric Neurology 11(2):90–95
44. Koelman DLH, Benkeser DC, Klein JP, Mateen FJ (2017) Acute disseminated encephalomyelitis: prognostic value of early follow-up brain MRI. J Neurol 264(8):1754–1762
45. Dubey D, Pittock SJ, Kelly CR et al (2018) Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol 83(1):166–177
46. Grzonka P, Scholz MC, De Marchis GM et al (2020) Acute Hemorrhagic Leukoencephalitis: A Case and Systematic Review of the Literature. Front Neurol 11:899
47. de Seze J, Debouverie M, Zephir H et al (2007) Acute fulminant demyelinating disease: a descriptive study of 60 patients. Arch Neurol 64(10):1426–1432
48. Sonneville R, Demeret S, Klein I et al (2008) Acute disseminated encephalomyelitisin the intensive care unit:clinical features and outcome of 20 adults. Intensive Care Med 34(3):528–532

Figures

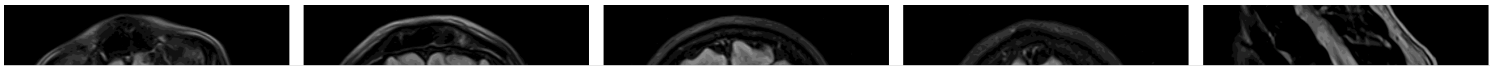

Figure 1

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.