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Acute Disseminated Encephalomyelitis in COVID 19- Systematic Review

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Abstract

Introduction: There has been a concerning increase in the prevalence of COVID-19 associated acute disseminated encephalomyelitis (ADEM). ADEM is a rare autoimmune disorder, often post-viral and primarily attacks children and can potentially lead to long-lasting neurological sequelae. As such, accurate diagnosis and timely management are of paramount clinical significance. Hence in the present study, we aim to determine the incidence, risk factors, clinical features, laboratory findings, management & fatality of ADEM in covid-19 patients.

Material And Methods**:** A systematic search adhering to PRISMA guidelines was performed from electronic databases (Medline, Google Scholar, OpenGray, Cochrane Library, NYAM) from inception until October 12, 2020. Renowned preprint servers like medRxiv, bioRxiv were also searched. Published case reports/series of proven/presumed ADEM in COVID-19 patients were included.

Results**:** Fourteen case reports/series were included. The mean age was 50.6±15.2 years, with a male to female ratio of 1:1. Most cases reported signs/symptoms of neurological nature prior to respiratory, the most common being: headaches, paresthesia, movement disorders, positive Babinski's sign and absent Deep tendon reflexes. Hypertension was the most common comorbidity.

Conclusions**:** Neurological symptoms were the main presentation of COVID-19, which did not correlate with the severity of respiratory symptoms. The high incidence of ADEM with hemorrhage (n=3) is striking. A rise in the prevalence of ADEM in adults in contrast to children is also concerning. Brain inflammation is likely caused by an immune response to the disease rather than neurotropism. Clinicians need to be vigilant as early diagnosis can improve patient outcomes.

Introduction

Coronavirus disease (COVID-19) is caused by the novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Since its recent discovery in Wuhan, China,

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coronavirus disease has spread globally, leaving physicians challenged by its variable clinical manifestations. Most patients infected by SARS-CoV-2 have presented with a mild clinical course: beginning with fever and dry cough, progressing to a form of mild or moderate respiratory disease, and resolving without specific treatment [2]. Serious complications of the infection, however, remain a central concern. Acute respiratory distress syndrome, acute heart injury or failure, acute kidney injury, sepsis, disseminated intravascular coagulation, and life-threatening metabolic derangements have all been reported in COVID-19 patients, particularly among those with underlying comorbidities or advanced age [1, 3] As knowledge of SARS-CoV-2 and its clinical appearance continue to grow, the literature has shown a significant number of infected patients exhibit neurological symptoms [4, 5].Hence in the present study, we aim to determine the incidence, risk factors, clinical features, laboratory findings, management & fatality of ADEM in covid-19 patients.

Material and methods

We searched the data from online sources like the "EMBASE", "Pubmed", "Scopus" and other sources. The study was conducted by two reviewers independently. The PRISMA guidelines were followed. The articles were collected from January 2020 to February 2021. The search words are Acute Disseminated Encephalomyelitis**,** COVID, COVID19, SARS, CoV2, neurological symptoms. The animal studies, population data, epidemiology, reviews were excluded along with the inconclusive diagnosis, other languages that cannot be translated to English. Total participants, sociodemographic, study type, clinical features, comorbidities were noted for all the studies. Statistical analysis was done, keeping the p value<0.05.

Results

Fourteen case reports/series were included after the application of the inclusion and the exclusion criteria. [Figure 1] Mean age was 50.6±15.2 years, with a male to female ratio of 1:1. Most cases reported signs/symptoms of neurological nature before respiratory, the most common being: headaches, paresthesia, movement disorders, positive Babinski's sign and absent Deep tendon reflexes. Hypertension was the most common comorbidity. Eleven patients required intubation. Treatment with high-dose corticosteroids and antibiotics/antivirals resulted in partial recovery of 66.6% of cases. Corticosteroids plus IVIG therapy aided in partial recovery of 27.7% of cases. Plasmapheresis was limited to 4 patients. SARS-CoV2 was reported in CSF samples of 11.1% of patients. Partial recovery was seen in 88.8%, and in-hospital mortality was reported in 11.1% of patients. Full clinical response was not seen. [Table 1]

TABLE 1: COMPARISON OF THE STUDIES

Publication	Total patients	Gender	Age (years)	Encephalitis	headaches,	paresthesia	movement disorders,	Babinski's sign	Deep tendon reflexes
Ellul	14	7 F/ 7 M	52.7	2/ 11	5/ 14	8/14	5 / 14	9/ 14	0

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Munhoz	22	113 F/ 108 M	55	22	22	22	22	22	0
Zhang	4	NA	63	4	4	4	4	4	0
Helms J	12	NA	NA	12	12	12	12	12	0
Panciani	6	1F/5M	68.5	6	6	6	6	6	0
Pohl D	21	12 F/ 9M	52.7	21	21	21	21	21	0
Krupp LB	22	11 F/ 11 M	55	22	22	22	22	22	0
Ketelslegers	6	NA	63	6	6	6	6	6	0
Kamr	14	1 F/ 13 M	52.7	14	14	14	14	14	0
Yeh	11	11 M	55	11	11	11	11	11	0
Arabi	6	NA	63	6	6	6	6	6	0
Mehta	12	7 F/ 5 M	52.7	12	12	12	12	12	0
Murray	14	3 F/ 11M	55	14	14	14	14	14	0
Novi	18	NA	63	18	18	18	18	18	0

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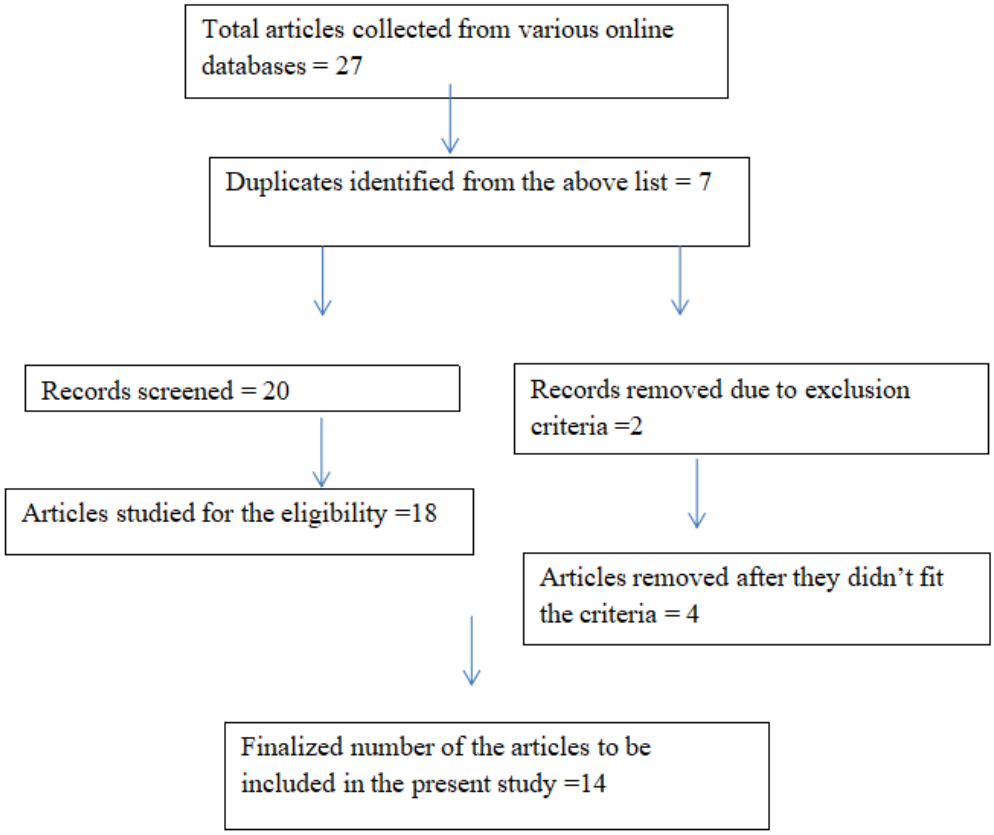
FIGURE 1. FLOW CHART DESCRIBING THE SELECTION OF THE ARTICLES



Discussion

The neurotrophic prospective of the coronaviruses has been widely documented since the original descriptions [7]. SARS-CoV-2 potential to cause neurological damage has been rapidly recognized as the present epidemic unfolded ARS-CoV-2 may reach the brain via the bloodstream or transcribriform route along the olfactory nerve [18]. The virus invades neurons through angiotensin-converting enzyme-2 (ACE-2) receptors. A maximum of SARS-CoV-2 neurological manifestations are thought to occur in late stages of the infection, possibly associated with immune response[8]. Neurological symptoms and neuroimaging findings in our cases could be caused by ischemic injuries, by a direct encephalitic viral effect, by toxic-metabolic insults or by an acute demyelination process. MRI diffusion images did not display diffusion constraint that resembles a vascular pattern, rendering ischemia unlikely. Additionally, CSF analysis was not indicative of an infectious process, neurological impairment was not present in the acute phase of the infection, and neuroimaging findings were not typical of classical toxic and metabolic disorders, making the first three elicited mechanisms unlikely. The finding of bilateral periventricular relatively asymmetrical lesions allied with deep white matter involvement suggests an acute demyelination process. We considered both cases well-matched with the diagnosis of acute disseminated encephalomyelitis (ADEM) related to COVID-19 disease, since the clinical presentation was encephalopathy and neuroimaging showed multifocal white matter abnormalities. Other

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clinical clues favouring this diagnosis are: prior confirmed acute viral infection, unremarkable CSF study excluding CNS infection, negative oligoclonal bands and lack of previous history of demyelinating diseases, such as multiple sclerosis, in both patients. ADEM is an acute inflammatory CNS demyelinating condition precipitated by viral infection or, more rarely, vaccination, and is categorized by encephalopathy and multifocal neurologic deficits [9,10]. Given the lack of specific biomarkers or confirmatory tests, the diagnosis of ADEM is based on combined clinical and radiological features and exclusion of other possible similar conditions [9,10]. In children, in whom ADEM is more frequently met, current diagnostic criteria require the presence of encephalopathy, multifocal CNS events, and acute MRI abnormalities [10,11]. Specific criteria for ADEM in adults have not been established. Due to lower incidence in adults, ADEM is less studied in this population. The largest study associating ADEM in different age groups showed that, in adults, disease course was more aggressive, and outcomes were poorer than in children [12].MRI is the favoured neuroimaging modality in patients with suspected ADEM since head CT can be normal or display non-diagnostic features. In these cases, brain MRI typically displays bilateral and asymmetric T2/FLAIR hyperintensities in central and subcortical white matter[9,10,] that may also be present in cortical gray-white matter junction, thalami, basal ganglia, cerebellum, and brainstem. Heterogeneous findings are frequently encountered. Up to one-third of patients may existing gadolinium-enhancing lesions, and up to one third may present spinal cord involvement[9.] Restricted diffusion in diffusion-weighted imaging (DWI) sequences can be present in acute settings and associated with a more aggressive disease course [13]. ADEM has already been reported in endemic coronavirus subtypes in preceding coronavirus outbreaks [14,15]. In 2004, a 15-year-old boy presented cerebellar and spinal cord demyelinating lesions with a preceding upper respiratory tract illness history. In 2015, a case report described a patient with slow awakening after prolonged ICU stay due to MERS-CoV infection, in whom brain MRI identified bilateral multifocal white matter lesions. The authors related those findings to ADEM, rather than to encephalitis, due to direct viral neuroinvasion, since CSF analysis dis-closed negative PCR for MERS-CoV[15]. Demyelinating lesions after viral infection can be caused by cross-reaction between immune response and host cell components, as well as by lymphocyte and macrophage reaction and lymphokine-mediated damage, and immune cell protease release16. The pro-inflammatory state in COVID-19 is associated with increased cytokines ("cytokine storm") that may activate glial cells, leading to demyelination[17,18]. Additionally, viral infection can trigger the production of antibodies targeted against glial cells[18]. In primates, murine coronavirus can intensely replicate and cause oligodendrocyte lysis and demyelination[19]. Perivenular sleeves of demyelination associated with inflammatory infiltrates are the hallmark of ADEM pathology[9]. Eventually, larger areas of demyelination may occur secondary to the coalescence of perivenous demyelinating lesions. Post-mortem neuropathological findings in one COVID-19 patient revealed features suggestive of combined demyelinating and vascular mechanisms. Additionally, hemorrhagic white matter lesions, clusters of macrophages related to axonal injury and ADEM-like appearance were also found in subcortical white matter[20]. We found three single case reports of suspected COVID-19 infection related to ADEM[3,21]. The largest COVID-19-associated ADEM series to date describes 43 patients with COVID-19-related neurological disorders, nine of whom were classified within the ADEM spectrum, with a broad range of clinical and radiological presentations[4]. None of the five tested patients presented positive for SARS-

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CoV-2 in the CSF. Four of the nine patients presented with critical or severe COVID-19 infection; in three, the initial neurological symptom was slow awakening in the ICU; eight underwent immunotherapies. Only one patient presented a complete recovery, seven showed improvement by the time the article was published, and one died. A neuropathological specimen obtained in a patient that underwent hemicraniectomy revealed findings supportive of ADEM; SARS-CoV-2 was not identified in brain tissue. All patients presented multifocal supratentorial white matter lesions, and two also disclosed intraspinal lesions[4]. The main characteristics of the three patients with slow awakening in ICU in that series [4] resemble those of the two patients presented here. These patients had more than two weeks of ICU stay, presented with severe respiratory distress due to confirmed COVID-19 infection, PCR for SARS-CoV-2 in CSF was negative in the tested ones, and MRI depicted multifocal areas of white matter lesions, some with hemorrhagic features. Additionally, one of these patients showed ongoing improvement with supportive treatment alone, similarly to the patient [2]. Treatment of ADEM consists of immunotherapies, such as intravenous pulse methylprednisolone, plasma exchange and Ig IV. There are no randomized controlled trials related to ADEM. The use of high-dose intravenous corticosteroids is widely accepted as first-line therapy and was associated with substantial clinical improvement in adults in uncontrolled observational studies[9,10]. In patients who fail to respond to corticosteroids, IgIV and, less commonly, plasma exchange is considered second-line options[24]. In COVID-19 patients, immunotherapy should be individualized, taking into account concerns about the safety of these treatments.COVID-19 infection-related ADEM described in the current literature presents heterogeneous clinical and neuroimaging findings. We have met reports that point to increasing ADEM diagnoses in a subgroup of patients that present with marked encephalopathy and disorders of consciousness after lengthy mechanical ventilation and ICU stay due to severe COVID-19 infection. The pathophysiology of this pattern of CNS lesions related to these conditions remains incompletely understood. An attractive explanation would be of an immune-mediated inflammatory reaction associated with the viral infection. Further studies should help elucidate the role of the viral infection and COVID-19-associated inflammatory states in the pathogenesis of brain lesions in this clinical setting. These two reported cases highlight the prominence of a careful neurological evaluation, followed by adequate neuroimaging, preferably MRI, in SARS-CoV-2 patients with delayed awakening after ICU stay. Disorders of consciousness are frequently credited to toxic-metabolic encephalopathy. In this setting, brain lesions can be missed, unless patients undergo brain imaging studies. The neurological impairment caused by ADEM may hurt long-term neurologic deficits, functional outcomes and mortality of patients with severe COVID-19 infections. Health professionals should be trained to promptly recognize neurologic manifestation in COVID-19 patients, allowing an early diagnosis of potentially treatable conditions and possibly minimizing neurological sequelae of COVID-19 infection

Conclusion

Neurological symptoms were the main presentation of COVID-19, which did not correlate with the severity of respiratory symptoms. The high incidence of ADEM with hemorrhage is striking. A rise in the prevalence of ADEM in adults in contrast to children is also concerning. Brain inflammation is likely caused by an immune response to the disease rather than neurotropism. Clinicians need to be vigilant as early diagnosis can improve patient outcomes.

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References

1. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020 Jul;19(9):767-83. https://doi.org/10.1016/s1474-4422(20)30221-0
2. Munhoz RP, Pedroso JL, Nascimento FA, Almeida SM, Barsottini OGP, Cardoso FEC, et al. Neurological complications in patients with SARS-CoV-2 infection: a systematic review. Arq Neuropsiquiatr. 2020 May;78(5):290-300. https://doi.org/10.1590/0004-282x20200051
3. Zhang T, Rodricks MB, Hirsh E. COVID-19-associated acute disseminated encephalomyelitis: a case report. Neurocrit Care. 2020 AprOct; 1-7. https://doi.org/10.1007/s12028-020-01119-74.
4. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020 Oct;143(10):3104-20. https://doi.org/10.1093/brain/awaa240References 2020;78(12):805-810
5. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med. 2020 Jun;382(23):2268-70. https://doi.org/10.1056/nejmc2008597
6. Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, et al. Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection [published online ahead of print, 2020 May 8]. Radiology. 2020 May;297(1):E232-5.. https://doi.org/10.1148/radiol.2020201697
7. McIntosh K, Becker WB, Chanock RM. Growth in suckling-mouse brain of "IBV-like" viruses from patients with upper respiratory tract disease. Proc Natl Acad Sci U S A. 1967 Oct;58(6):2268-73. https://doi.org/10.1073/pnas.58.6.2268
8. Panciani PP, Saraceno G, Zanin L, Renisi G, Signorini L, Battaglia L, et al. SARS-CoV-2: "Three-steps" infection model and CSF diagnostic implication. Brain Behav Immun. 2020 Jul;87:128-9. https://doi.org/10.1016/j.bbi.2020.05.002
9. Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Tenembaum S, et al. Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. Neurology. 2016 Aug;87(9 Suppl 2):S38-45. https://doi.org/10.1212/wnl.0000000000002825
10. Pohl D, Evans E, Mwangi M, Mar S. Acute Disseminated Encephalomyelitis in Children: An Updated Review Based on Current Diagnostic Criteria. Pediatr Neurol. 2019 Jul;100:26-34. https://doi.org/10.1016/j.pediatrneurol.2019.06.017
11. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013 Apr;19(10):1261-7. https://doi.org/10.1177/1352458513484547
12. Ketelslegers IA, Visser IE, Neuteboom RF, Boon M, Catsman-Berrevoets CE, Hintzen RQ. Disease course and outcome of acute disseminated encephalomyelitis is more severe in adults than in children. Mult Scler. 2011 Dec;17(4):441-8. https://doi.org/10.1177/1352458510390068
13. Kamr, W.H., Tantawy AM, Moustafa M, Adb-Elsalam OA. Acute disseminated encephalomyelitis: MR Diffusion weighted imaging: Potential diagnostic value and

outcome predilection. The Egyptian Journal of Radiology and Nuclear Medicine, 2017 Mar;48(1):215-23. https://doi.org/10.1016/j.ejrnm.2017.01.004.
14. Yeh EA, Collins A, Cohen ME, Duffner PK, Faden H. Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. Pediatrics. 2004 Jan;113(1 Pt 1):e73-6. https://doi.org/10.1542/peds.113.1.e73
15. Arabi YM, Harthi A, Hussein J, Bouchama A, Johani S, Hajeer AH, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection. 2015 Jan;43(4):495-501. https://doi.org/10.1007/s15010-015-0720-y
16. Barac-Latas V, Suchanek G, Breitschopf H, Stuehler A, Wege H, Lassmann H. Patterns of oligodendrocyte pathology in coronavirus-induced subacute demyelinating encephalomyelitis in the Lewis rat. Glia. 1997 Dec;19(1):1-12. https://doi.org/10.1002/(sici)1098-1136(199701)19:1%3C1::aid-glia1%3E3.0.co;2-5
17. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar;395(10229):1033-4. https://doi.org/10.1016/s0140-6736(20)30628-0
18. Caso F, Costa L, Ruscitti P, Navarini L, Del Puente A, Giacomelli R, et al. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? Autoimmun Rev. 2020 May;19(5):102524. https://doi.org/10.1016/j.autrev.2020.102524
19. Murray RS, Cai GY, Hoel K, Zhang JY, Soike KF, Cabirac GF. Coronavirus infects and causes demyelination in primate central nervous system. Virology. 1992 May;188(1):274-84. https://doi.org/10.1016/0042-6822(92)90757-G
20. Reichard RR, Kashani KB, Boire NA, Constantopoulos E, Guo Y, Lucchinetti CF. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. Acta Neuropathol. 2020 May;140(1):1-6. https://doi.org/10.1007/s00401-020-02166-2
21. Novi G, Rossi T, Pedemonte E, Saitta L, Rolla C, Roccatagliata L, et al. Acute disseminated encephalomyelitis after SARS-CoV-2 infection.Neurol Neuroimmunol Neuroinflamm. 2020 Jun;7(5):e797. https://doi.org/10.1212/nxi.0000000000000797
22. Parsons T, Banks S, Bae C, Gelber J, Alahmadi H, Tichauer M. COVID-19-associated acute disseminated encephalomyelitis (ADEM). J Neurol. 2020 May;267(10):2799-802. https://doi.org/10.1007/s00415-020-09951-9
23. McCuddy M, Kelkar P, Zhao Y, Wicklund D. Acute Demyelinating Encephalomyelitis (ADEM) in COVID-19 infection: A Case Series.2020 Sep-Oct;68(5):1192-5. https://doi.org/10.1101/2020.07.15.20126730.
24. Marchioni E, Marinou-Aktipi K, Uggetti C, Bottanelli M, Pichiecchio A, Soragna D, et al. Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis. J Neurol. 2002 Jan;249(1):100-4. https://doi.org/10.1007/PL00007836