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Short Communication

Covid-19 systemic infection exacerbates pre-existing acute disseminated encephalomyelitis (ADEM)

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ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is an uncommon diagnosis in adults. It is known to be due to an abnormal immune response to a systemic infection rather than direct viral invasion to the central nervous system. There have been few reports of ADEM diagnosed in the setting of COVID-19 systemic infection. However, we report a case of Coxsackie induced ADEM that remitted but got exacerbated by COVID-19 infection. The patient contracted the COVID-19 infection shortly after being discharged to a rehabilitation facility. Direct COVID-19 neuroinvasion was ruled out via CSF PCR testing for the virus. The patient responded well to pulse steroid therapy and plasmapheresis in both occasions. We hypothesize that COVID-19 infection can flare-up a recently remitted ADEM via altering the immune responses. It is known now that COVID-19 infection can produce cytokine storming. Cytokine pathway activation is known to be involved in the pathology of ADEM. Caution regarding discharging immune suppressed patient to the inpatient rehabilitation facility should be made in the era of COVID-19 pandemic.

1. Introduction

According to a recent brief report, acute encephalopathy in COVID-19 infected patients was the leading neurological symptom among those of the central nervous system (CNS) and the second among all neurological symptoms (after the nonspecific myalgia) (Agarwal et al., 2020).

Acute encephalopathy associated with COVID-19 infection is frequently under-investigated and in many cases is attributed to metabolic causes. However, more specific etiologies exist. Seizures, diffuse +/− focal cerebral hypoxia, reversible cerebral vasoconstriction syndrome, acute (para-infectious) disseminated encephalomyelitis (ADEM), and direct viral encephalomyelitis are all reported conditions that should be considered in a COVID-19 patient who becomes acutely encephalopathic with or without focal manifestations (Koralnik and Tyler, 2020; Hepburn et al., 2020; Anand et al., 2020; Reichard et al., 2020; Parsons et al., 2020; Abdi et al., 2020). Clinical management and prognosis differ according to the underlying pathology.

2. Case report

A 55-year-old African-American female with a history of hypertension, alcohol abuse, and right-side weakness due to an untreated severe cervical disc herniation presenting with severe confusion and mumbling of two-day duration. Her neurological examination was significant for poor mental status in all aspects (Glasgow coma scale [GCS] of 9 [eye = 2, voice = 2, Motor = 5]). She also had generalized right > left weakness (localizing with the left arm, mildly withdrawing with the right arm, and both lower extremities). Her initial laboratories showed hypoglycemia (50 mg/dL), hyponatremia (127 mmol/L), and severe microcytic anemia (hemoglobin of 5.5 g/dL). These electrolyte derangements were corrected appropriately. She was given intravenous injection of 50% Dextrose, started on intravenous infusion of normal saline and regular tube feeds through a nasogastric tube, and transfused two units of packed red blood cells. However, despite these measures, her mental status did not improve. She had normal thyroid functions. Her serum vitamin and mineral levels were normal. Her basic infectious workup was negative, including COVID-19 testing. A continuous video-electroencephalogram (EEG) showed fluctuating left hemispheric sharp and slow wave periodic discharges, occurring at 1–2 Hz. It was

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; CT, computed tomography; FLAIR, fluid attenuated inversion recovery; RT-Quic, Real-time quaking-induced conversion; PCR, polymerase chain reaction; IVIG, intravenous immunoglobulins; RCVS, reversible cerebral vasoconstriction syndrome;; PRES, posterior reversible encephalopathy syndrome.

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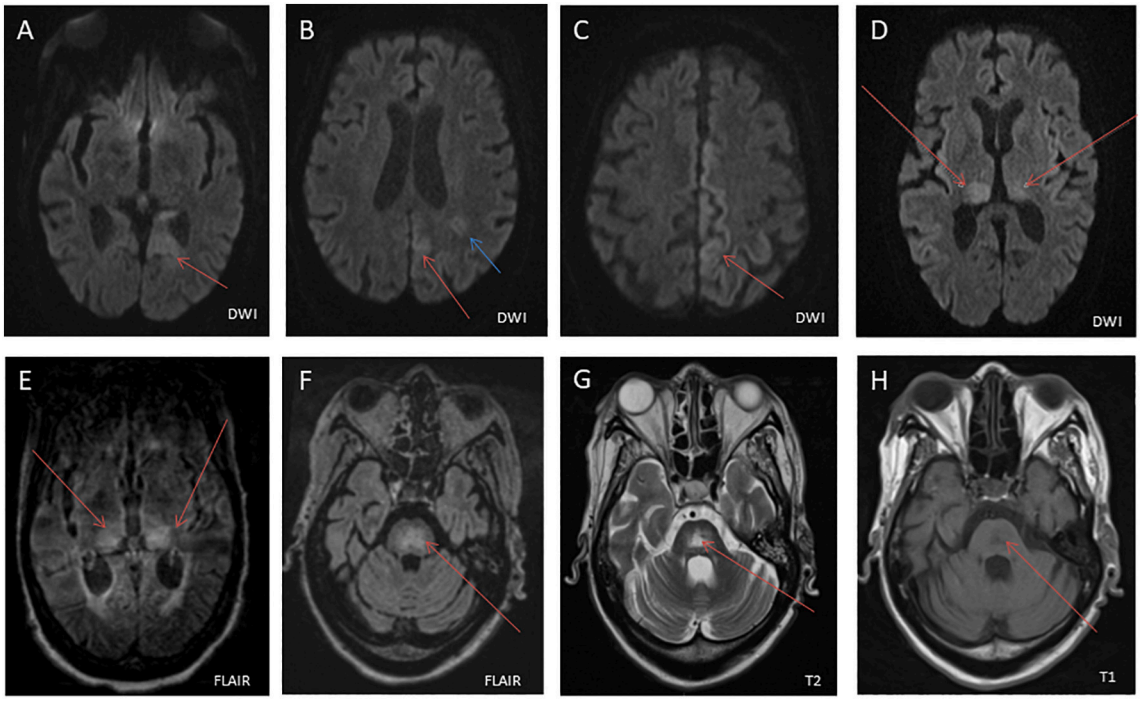

Fig. 1. Disseminated cortical and subcortical lesions throughout the brain which were seen in the initial presentation. Image A shows a restricted diffusion lesion in the left retrosplenial region (red arrow). Image B shows restricted diffusion in the left occipital cortex (red arrow) as well as the left optic radiation white matter (blue arrow). Image C shows restricted diffusion in the parasagittal cortex, mainly on the left (red arrow). Image D shows restricted diffusion in both thalami (red arrows). Image E demonstrates the bilateral thalamic lesions on the FLAIR sequence (red arrows). Image F and G show central mid-pontine hyperintense lesion on FLAIR and T2 sequences respectively (red arrows). Image H demonstrates the mid-pontine lesion as a hypodense area on the T1 sequence (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

associated with occasional right arm jerking movements, thus, considered seizures. Levetiracetam, 1500 mg BID, improved her seizures. Her poor mentation persisted. Brain Magnetic resonance imaging (MRI) showed mild asymmetric restricted diffusion in the left > right cerebral cortex (cortical ribboning fashion), thalami, the left subsplenial region, the left subcortical optic radiations and the mid pons. These lesions also showed on T2 and FLAIR sequences as hyperintensities without enhancement on T1 with contrast (Fig. 1). CT-angiogram did not show evidence of intracranial vasospasms, endothelialitis, or vasculitis. Extensive serum and cerebrospinal fluid analyses were only positive for elevated serum Coxsackie-B type 4 viral IgG neutralizing antibody titers (titers initially were 1:80 then rose to 1:160 then to 1:320 on subsequent testing more than 10 days apart from each other). Workup has also included: a) viral, fungal, and bacterial infection testing (including *tropheryma whipplei*), b) anti-ganglioside, autoimmune, paraneoplastic, thyroid, and celiac antibody testing, and c) prion protein testing (RT-Quic). Eventually, she was diagnosed with acute disseminated encephalomyelitis (ADEM) based on the disseminated brain lesions, severe encephalopathy, seizures, and a lack of direct viral neuro-invasion. The patient received a five-day course of pulse-steroid therapy. A repeat-MRI showed improvement of the prior lesions and the appearance of a new symmetric pontine lesion (figure-1A). She further received seven sessions of plasmapheresis. Her mentation and speech have remarkably improved over a course of 3 weeks (GCS = 15). Another repeat-MRI showed near-resolution if her lesions (Fig. 2). Before discharge to an inpatient rehabilitation facility, she tested negative for the COVID-19 virus.

Three days later, the patient returned with a recurrence of her severe encephalopathy associated with fever. She tested positive for COVID-19 (tested via polymerase chain reaction [PCR] technique of a nasopharyngeal and oropharyngeal swabs). She was intubated due to the progressive worsening of her mental (GCS = 6; eye = 1, verbal = 1, motor = 4) and respiratory statuses. EEG showed new right posterior periodic polyspike waves that occasionally evolved into brief clinico-electrographic focal seizures. Lacosamide 200 mg BID followed by topiramate 150 mg BID were added to control the seizures. Brain-MRI showed flare-up of the previous lesions along with new lesions (Fig. 3). Her CSF tested negative for COVID-19 (tested using PCR technique at the University of Washington, Seatle, USA) indicating a lack of direct neuro-invasion. The patient received 2 g of intravenous immunoglobulins (IVIG) over 5 days. She had mild improvement. She received a tracheostomy tube due to persistent increased respiratory secretions in the setting of persistent encephalopathy. She received another course of pulse-steroid therapy and 7 sessions of plasmapheresis over a course of 2 weeks. Her tracheostomy tube was weaned off. Her mental status remarkably improved as evidenced clinically and electrographically. A repeat-MRI showed some persisting lesions. She was maintained on oral prednisone (60 mg daily) with a plan to slowly taper over 2 months.

3. Discussion

ADEM is an autoimmune disease that is characterized clinically by acute to subacute encephalopathy with or without other symptoms. It is characterized radiologically by disseminated subcortical white matter and deep grey matter lesions. It is usually linked to a recent viral or bacterial infection. In our case, the patient had a recent systemic coxsackie B type 4 infection. The IgG neutralizing antibodies in the serum were positive. Policies indicate that single positive antibody titers of greater than or equal to 1:80 may indicate past or current infection. Seroconversion, an increase, or a decrease in the titers of at least four folds is considered strong evidence of current or recent infection (Grist and Bell, 1973; Bell and McCartney, 1984). Our patient had a fourfold rise in her titers as shown in the case.

The presence of brain lesions with a lack of clinical improvement after correction of the mild metabolic derangements exclude metabolic

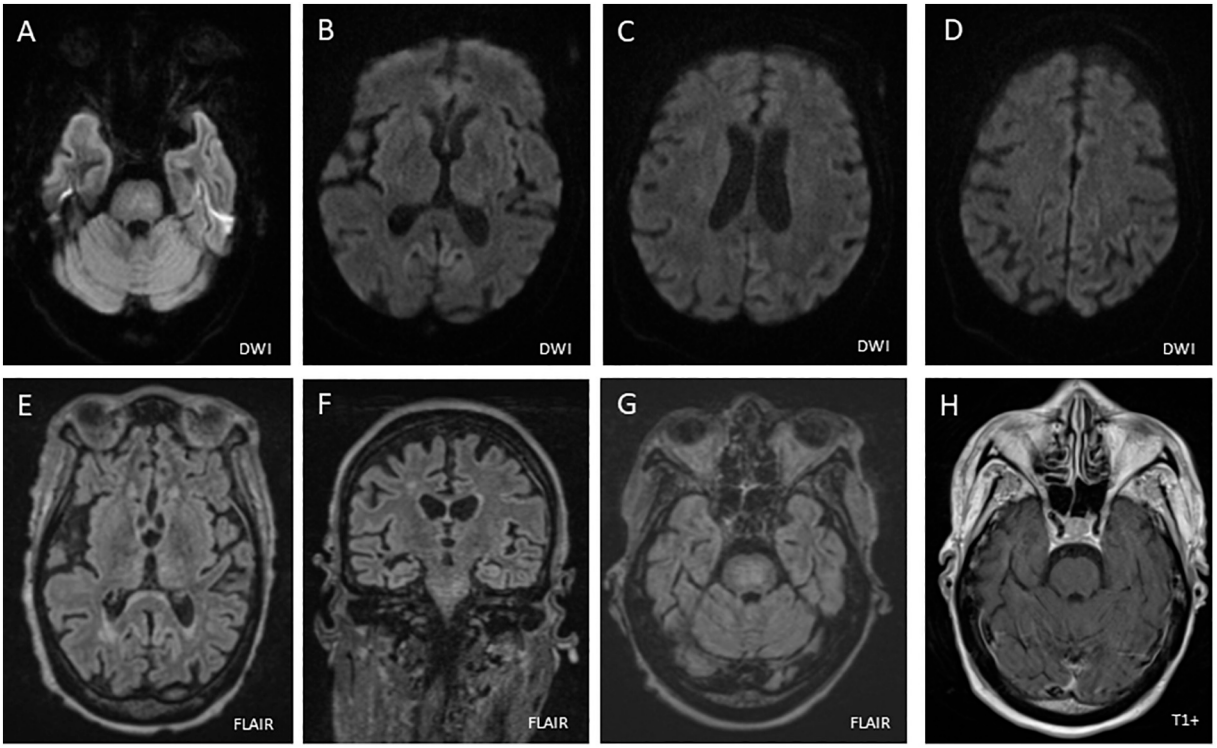

Fig. 2. Different MRI sequences showing a near resolution of the previously demonstrated lesions in Fig. 1. This occurred in response to treatment with pulse steroid therapy and plasmapheresis as described in the case. These were accompanied by improvement in mental status.

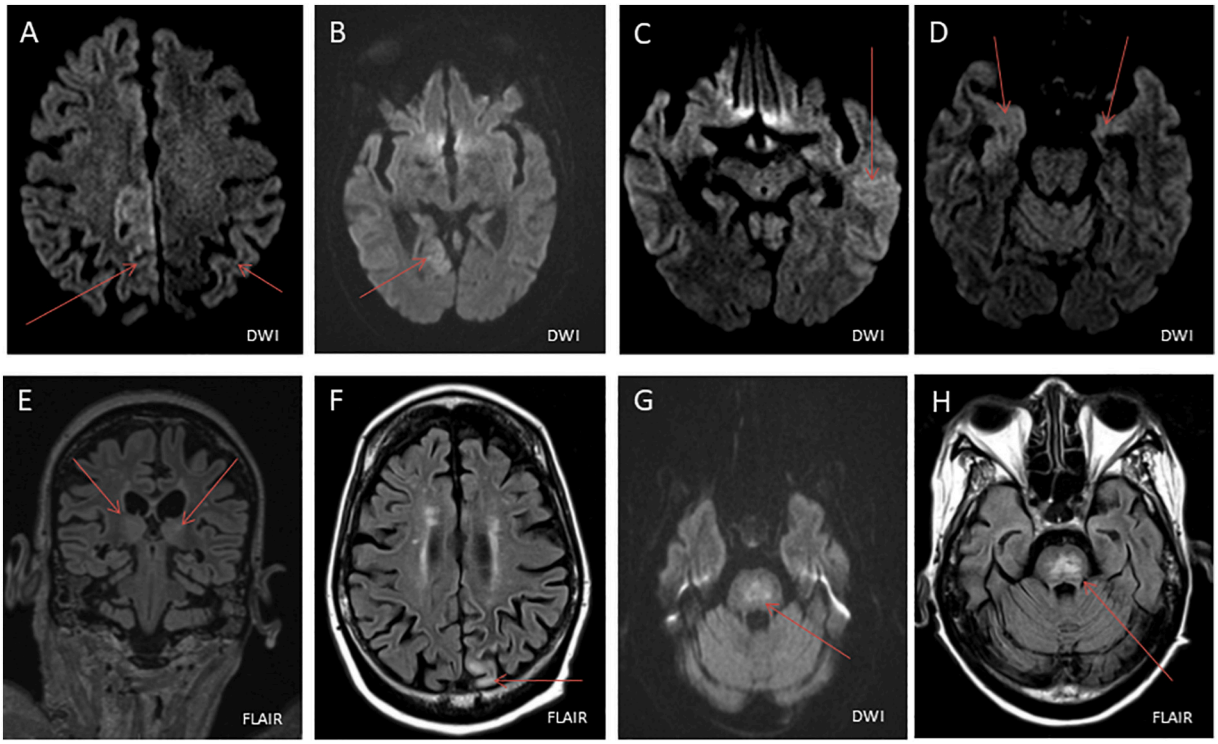

Fig. 3. Different MRI sequences demonstrating exacerbation of the previously seen lesions in Fig. 1 as well as the appearance of newer lesions. As seen, the lesions are cortical and subcortical. Images A-D shows new restricted diffusions in disseminated locations. Image E shows bi-thalamic mild hyperintensities on FLAIR which were not present in Fig. 2 Image F that demonstrated resolution of these lesions. Image F demonstrates a new FLAIR lesion in the left occipital cortex. Images G and H demonstrate the reappearance of the pontine lesions.

encephalopathy per se as the sole cause of her severe encephalopathy. While cortical ribboning diffusion restriction can be a consequence of seizures, the other multiple focal grey and white matter lesions and the bilaterality of the cortical ribboning exclude focal seizures as the sole etiology of encephalopathy. Besides, these lesions do not follow a vascular territory with a fluctuating diffusion restriction pattern making ischemia less likely. The locations of these lesions are anterior and posterior, supratentorial and infratentorial in addition to lack of vascular spasms or leakage (enhancement) making RCVS, posterior reversible encephalopathy syndrome (PRES), and vasculitis less likely. All autoimmune and paraneoplastic panels were negative. These panels included but were not limited to anti-NMDA, anti-GABA, anti-GAD 65, anti-AMPA, and anti-LGI1 antibodies. These were tested on the initial presentation and on the subsequent presentation with COVID-19 infection. Thus, we are left with two possible causes: infectious (direct viral invasion) versus parainfectious (ADEM). The main distinctive feature is whether the virus exists in the CSF or not. It did not. Finally, our case responded well to steroids and plasmapheresis.

ADEM is usually a diagnosis of childhood and is rarely diagnosed in adults. This might be due to underdiagnosed or misdiagnosed cases in adults. ADEM is usually a monophasic disease; however, it can be multiphasic on rare occasions. Nonetheless, our case should be considered monophasic as the exacerbation after improvement occurred within less than three months. This is according to the most recent diagnostic criteria. The only required symptom for diagnosis is acute or subacute encephalopathy which can range from behavioral changes to coma (Hussein and Minagar, 2017).

ADEM lesions are typically bilateral and asymmetric but occasionally are symmetric especially in the subcortical deep grey matter structures. In fact, symmetric lesions are more commonly seen in ADEM than in other autoimmune diseases. It can only affect the deep grey matter structures. The lesions usually have poorly-defined margins and are relatively large. Our case had some symmetric or semi-symmetric lesions (thalami and pons) and other disseminated lesions (cortical and subcortical). ADEM affect frequently the thalami and the basal ganglia (Hussein and Minagar, 2017; Hynson et al., 2001; Stonehouse et al., 2003). When ADEM affects the brain stem, it is more common in the midbrain and/or the pons and is usually central and symmetric (Lu et al., 2011). If occurred alone, it can mimic central pontine myelinolysis. However, our patient's sodium did not drop significantly and was not corrected quickly. While central myelinolysis can occur outside the pons, it is unlikely to be this extensive and to respond to immune-modulatory therapy. ADEM lesions usually appear as hyperintense lesions on T2 and FLAIR sequences and hypodense lesions on T1 sequence. It rarely enhances. Few studies have shown that about 45% of ADEM lesions show restricted diffusion. These cases usually have a more complicated course. Our patient did. It has been hypothesized that early restricted diffusion of ADEM lesions are due to myelin sheath cell edema and inflammation associated with decreased vascularity (Balasubramanya et al., 2007; Kamr et al., 2017).

ADEM pathophysiology is thought to be related to the antigenic mimicry theorem in genetically susceptible patients. In other words, a recent viral or bacterial infection leads to stimulation of the immune system, specifically the T-helper2 (Th2) lymphocytes and neutrophils, which results in the release of excessive cytokines and chemokines (Hussein and Minagar, 2017; Ishizu et al., 2006). COVID-19 infection has been linked to causing cytokine storms affecting the central nervous system (Mangalmurti and Hunter, 2020). By linking the two theories together, it seems logical to conclude that COVID-19 infection may result in an exacerbation of an existing ADEM attack. This, of course, does not deny that COVID-19 systemic infection can cause ADEM by itself. However, our case is unique. The patient was diagnosed with ADEM before the COVID-19 infection. She recovered her ADEM attack as proven clinically, electrographically, and radiologically (Fig. 2). However, her ADEM was exacerbated again (Fig. 3) after she contracted systemic COVID-19 infection without direct central nervous system invasion. In both attacks, she responded well to pulse steroid therapy and plasmapheresis. Without the distinction between ADEM and direct neuro-invasion of COVID-19 to the CNS, the patient would have not received her immune-modulatory therapy which might have led to decreasing her chances for better recovery and lesser complications.

Finally, ADEM and other autoimmune diseases are known to cause disabilities and usually require a good rehabilitation program after the initial recovery. However, in the era of COVID-19 infection, these strategies might not be the best for the patient after weighing the high risks of contracting the COVID-19 infection in such rehabilitation facilities versus the benefit of recovering the nerve and muscle functions. Adapted strategies based on the severity of the disabilities have been proposed (Treger et al., 2020).

Limitations: This is a case report to highlight an exciting observation of an exacerbated pre-existing ADEM attack in the setting of a new COVID-19 infection without central nervous system invasion. While we think our observation is interesting, it is without doubt that this might have happened by chance, Thus, we recommend that similar cases to be further studied and meta-analyzed among several centers dealing with such cases.

Our initial diagnosis of ADEM has met all the criteria of diagnosis. However, the predominant involvement of the cortex in ADEM is not the typical presentation of such disease. ADEM mostly involves subcortical white matter disease. Nonetheless, our case had some smaller involvement of the subcortical white matter (Fig. 1-B) but was not the dominant feature.

Disclosure

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Supplemental data

None.

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