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Brief Report

Clinicoradiological and prognostic features of COVID-19-associated acute disseminated encephalomyelitis



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ABSTRACT

Introduction. – The Covid-19 pandemic has resulted in a spark in interest in the subject given the high exposure rate to viral antigens in the form of infections and vaccines. It is expected that acute disseminated encephalomyelitis (ADEM) cases see a rise in incidence during this period. Given the plethora of Covid-19-related central nervous system (CNS) involvement, it is important to be aware of the varied presentations of ADEM.

Case reports. – In this paper, we report 3 cases of ADEM following Covid-19 infection. Patients presented with polyfocal neurological symptoms 6 to 18 days after respiratory symptoms onset. The diagnosis of Covid-19 was made based on nasal swab reverse transcriptase-polymerase chain reaction (RT-PCR) and chest computerized tomography (CT).

Discussion. – These cases illustrate both classic and atypical presentations requiring exclusion of a spectrum of CNS conditions to be able to retain the diagnosis of ADEM. Consequently, we stress the importance of context, clinical examination and MRI findings in the differentials. In addition, we discuss workup, and particularly, the indication of brain biopsy. Also, the paper discusses options in therapy and the prognosis. The prognosis of covid-associated ADEM is dependent on the extent of pathology intrinsic to ADEM and the intrication of the prognosis of Covid-19 infection.

Conclusion. – The key message in these 3 cases is that clinicians should have a low threshold of suspicion of ADEM in the Covid-19 context, adopt appropriate workup strategies, and initiate adequate treatment for better outcomes.

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1. Introduction

Acute disseminated encephalomyelitis (ADEM) is an acute, rapidly progressing immune-mediated demyelinating disorder of the central nervous system (CNS) characterized by acute polyfocal neurological manifestations and evidence of diffuse demyelination on neuroimaging [1]. The immune response is due to a post-infection or post-vaccination exposure to antigens from a pathogen leading to cross reaction with CNS myelin by molecular mimicry [2–4].

Importantly, however, neurological manifestations associated with Covid-19 are multifaceted and require a knowledge of their spectrum in addition to the myriad presentations of ADEM. Both central and peripheral neurological manifestations have been reported to be associated with Covid-19 [5]. If so, it is important for the clinician managing Covid-19 cases to be aware of the manifold presentation of ADEM, and have a low threshold of suspicion of the diagnosis. With three illustrative cases, we share some particulars of Covid-associated ADEM with respect to clinical presentation, radiological findings, treatment and outcomes.

2. Case presentations

2.1. Case report no. 1

A previously healthy 58-year-old man was seen in neurological consultation for dizziness and weakness of the lower limb. Neurological symptoms started 7 days before consultation, and were comprised of a rapidly progressive onset of vertigo, weakness associated with a left lateropulsion and numbness of the lower limbs. These symptoms were preceded by a flu-like syndrome that started 10 days before admission and were associated with nausea and vomiting. During this period the patient reported a feverish feeling. The clinical examination on admission showed normal vital signs: blood pressure 123/68 mmHg, heart rate 77 bpm, respiratory rate 19 bpm and body temperature of 37.7 °C. The neurological examination revealed a left central vestibular syndrome comprising vertigo and left lateropulsion, and diminished patella reflex. The other reflexes were normal. There was no weakness or sensory deficit and the rest of the neurological examination was unremarkable.

Based on the context of the pandemic, Covid-19 infection was suspected. A CT (computed tomography) of the chest was performed which showed subpleural ground-glass opacities with a bilateral crazy paving aspect (Fig. 1) typical of Covid-19 pneumonia with a positive nasal swab reverse transcriptase-polymerase chain reaction (RT-PCR). Brain MRI revealed hyperintense lesions in the right thalamus, left cerebellar and right parietal regions on the fluid-attenuated inversion recovery (FLAIR) weighted images (Fig. 2). The cerebrospinal fluid (CSF) analysis were normal, clear and colorless fluid, normal protein level, 0.59 g/L (normal range: 0.15–0.60 g/L), glucose level, 0.72 g/L (normal range: 0.54–0.72 g/L), 7 white blood cells, and no germs detected. Immunoelectrophoresis of serum and CSF revealed no oligoclonal bands and SARS-COV serology in CSF was negative. The Electroneuromyography (EMG) of the 4 limbs was normal

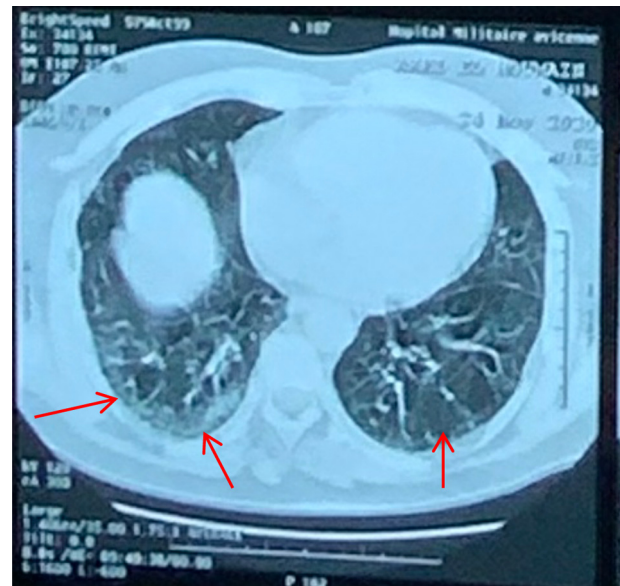


Fig. 1 – Axial chest CT showing subpleural ground glass opacities (red arrows) with bilateral crazy paving aspect.

and the remaining laboratory tests (complete blood count (CBC), serum biochemistry, C-reactive protein (CRP), urea, creatinine, liver function, thyroid function tests) were normal.

The diagnosis of Covid-19-associated acute disseminated encephalomyelitis (ADEM) was retained and the patient received a 5-day course of intravenous methylprednisolone (1 g per day for 5 days), followed by oral prednisone 1 mg/kg/day, which was then gradually tapered over 10 weeks. The Outcome was favorable with rapid regression of the symptoms, and the patient was completely asymptomatic after 6 weeks. A brain MRI performed 15 days after full recovery, was completely normal (Fig. 3).

2.2. Case report no. 2

A 25-year-old male without personal or family history of neurological disease was hospitalized for respiratory distress after 6 days of fever and cough. Covid-19 was diagnosed based on reverse-transcriptase PCR positive results on nasal swab and on findings of bilateral ground-glass opacities on thoracic CT scan. At day 12, the patient was weaned off oxygen and respiratory SARS CoV-2 RT-PCR was negative on day 13 of illness.

Five days after, the patient was found groaning and presented with rhythmic movements of the right upper limb, vertigo and falls. He was admitted in intensive care unit (ICU). His admission Glasgow Coma Score (GCS) was 14/15 (E4V4M6); he answered questions correctly but with latency. Romberg's sign was positive with tendency to fall backwards. No other neurological deficits were found on admission. Standard physical examination, including blood pressure and pulse, as well as blood chemistry was normal. Blood pressure was 132/77 mmHg, heart rate was 98 beats per minute, respiratory rate was 18 cycles per minute, and body temperature was 37.2 °C.

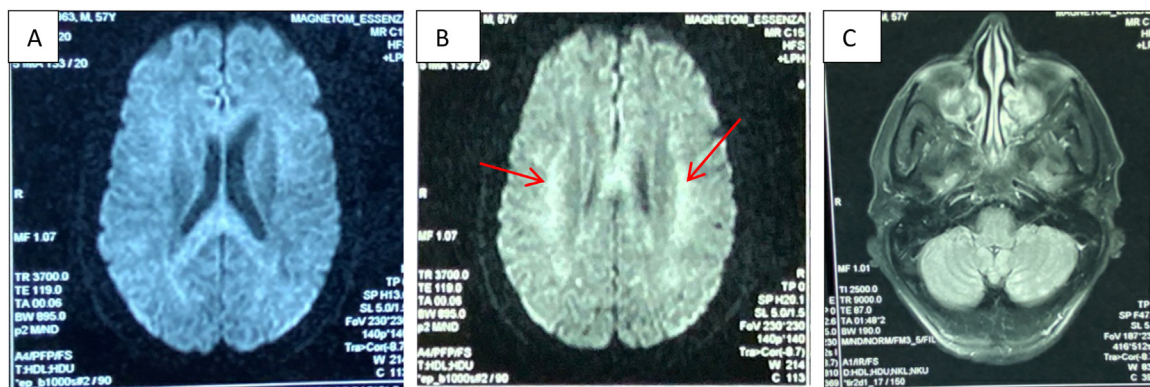


Fig. 2 – Brain MRI (FLAIR for A and B, diffusion for C) showing hyperintense lesions involving cortico-subcortical regions of both hemispheres, left hemisphere of cerebellum, the right parietal lobe and the left thalamus.

The patient's laboratory workup showed white blood cells: $10.550/\text{mm}^3$ (normal range: 4–10.5); hemoglobin, 16.7 g/dL, lymphopenia $920/\text{mm}^3$. Inflammatory markers were markedly elevated: LDH 798 U/L (normal range: 140–280 U/L), Ferritin $2575 \mu\text{g/L}$, CRP 59 mg/L (normal range $< 5 \text{ mg/L}$), D-dimer $> 9 \text{ mg/L}$ (normal range $< 5 \text{ mg/L}$), serum creatinine level, sodium and potassium levels, hemostasis workup, TSH and T4 levels were within normal range. CSF was clear and colorless. The CSF cell count was $1/\text{mm}^3$ mononuclear cells without red

blood cells. Serology for hepatitis B and C, toxoplasmosis, HIV and syphilis were negative.

Radiological evaluation with contrast CT scan of the brain showed hypodensities with finger in glove contrast enhancement, and hemorrhagic appearance of the left parietal lesion (Fig. 4). MRI of the brain showed a left temporal and bilateral fronto-parietal hyperintense lesions in T2-weighted and FLAIR images, dilation of the ventricular system more marked on the left. Three hyperintense lesions in FLAIR weighted lesions were found, in bilateral frontal and left parietal regions, surrounded by a hypointense corona, with T2 signal voids related to hematomas, the most voluminous being in the left frontal lobe. Multiple punctiform signal voids in T2 of the two cerebral hemispheres and vermis were also observed (Fig. 5).

On day 2 of his admission in critical care, stereotaxic brain biopsy was done using left pre-coronal frontal access. Seven biopsies were performed for histological examinations which demonstrated demyelination and perivenular inflammation without signs of a neoplasm.

On day 7, the patient's condition deteriorated further, with Glasgow Coma Scale of 5 (E1, V1, M3). Due to the worsening clinical and neurological status, the patient was intubated and started on intravenous methylprednisolone 1 g, based on a working diagnosis of Covid-19 related encephalitis, and died on the same day.

2.3. Case report no. 3

A 54-years-old female without personal or family history of neurological disease presented at the ER with dyspnea and cough associated with headache and fever. Nine days after the beginning of this symptomatology the patient developed a loss of balance, numbness of the four limbs and altered level of consciousness. The clinical examination showed normal vital signs: blood pressure = 13/8cmHg, heart rate = 64 beats per minute, respiratory rate = 20 cycles per minute, T = 38.7°C . The neurological examination revealed a confused patient with a mild GCS noted at 13, a spastic quadriplegia dominant on the left side of the body with muscle strength noted at 3/5 on the right half and 1/5 on the left half and a severe left-sided static and kinetic cerebellar syndrome.

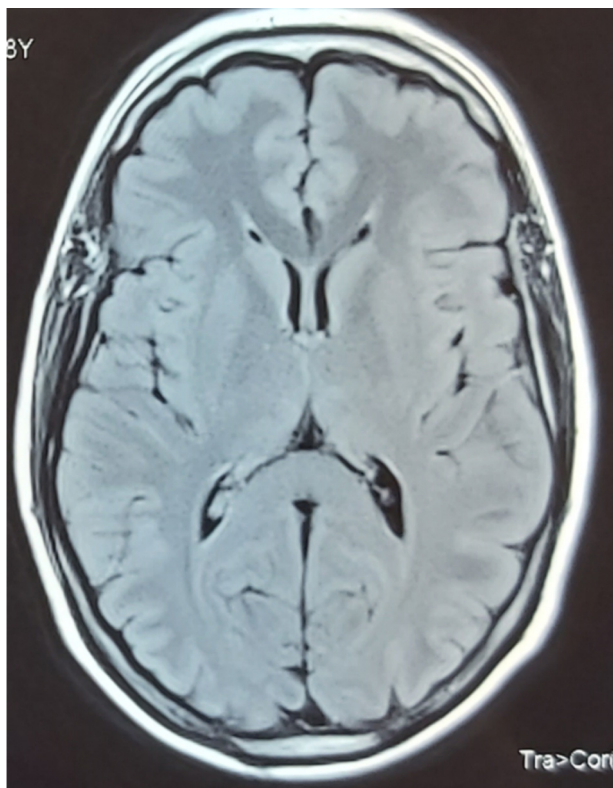


Fig. 3 – Brain MRI, Axial FLAIR-weighted image, showing the disappearance of the hyperintense lesions previously noted.

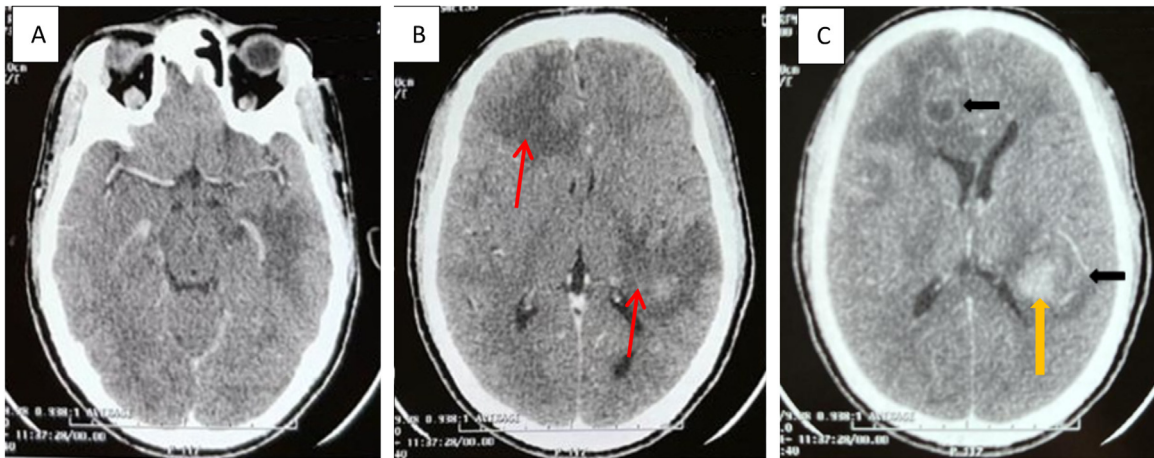


Fig. 4 – Contrast CT of the head on admission to hospital (day 0). Axial images show hypodensities (B, red arrows) with finger in glove contrast enhancement (C, black arrows) and hemorrhagic appearance of the left parietal lesion (C, yellow arrow).

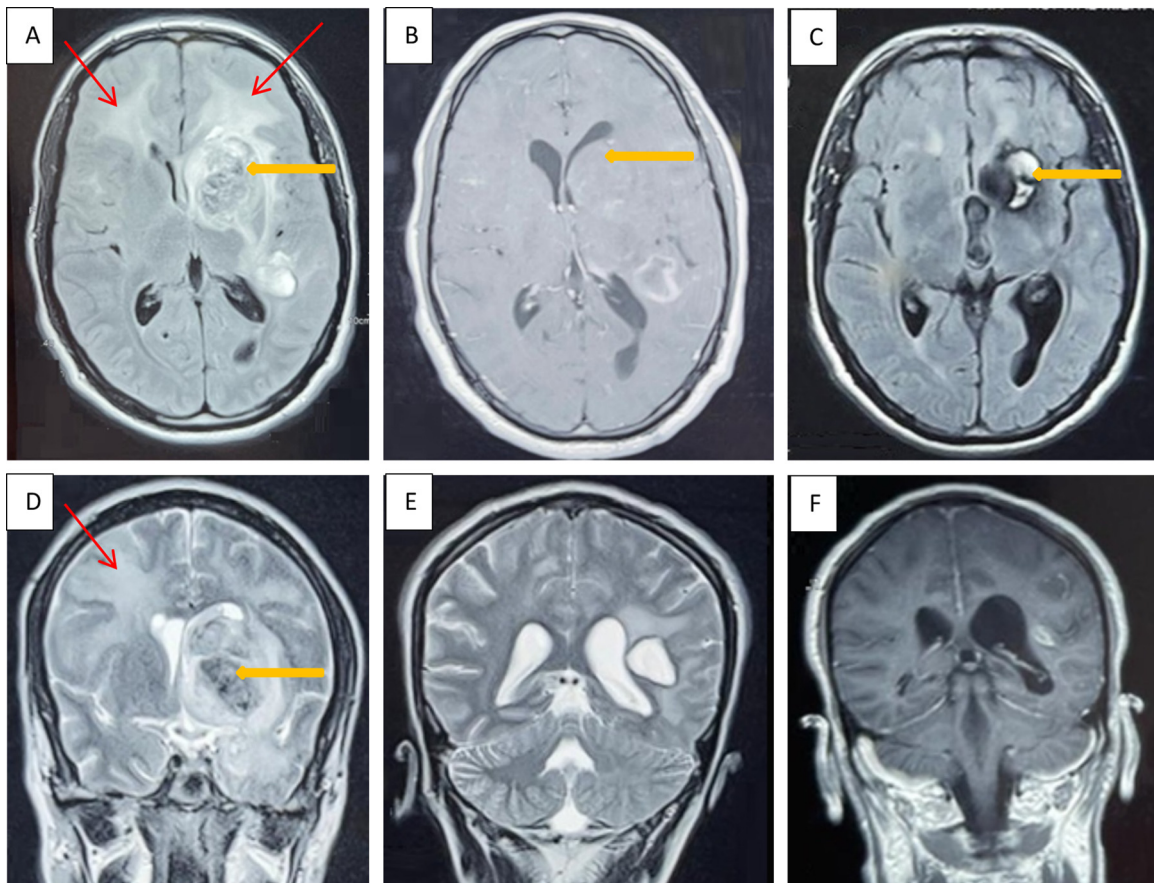


Fig. 5 – MRI of the brain on day 2. Axial (A, B, C) and coronal (D, E, F) images showed hyperintense lesions in left temporal and bilateral fronto-parietal regions in FLAIR and T2 weighted images (red arrows). We also noted three hyperintense lesions, involving bilateral frontal and left parietal regions, surrounded by a hypointense corona, with signal voids related to hematomas, the most voluminous being in the left frontal lobe (Yellow arrows).

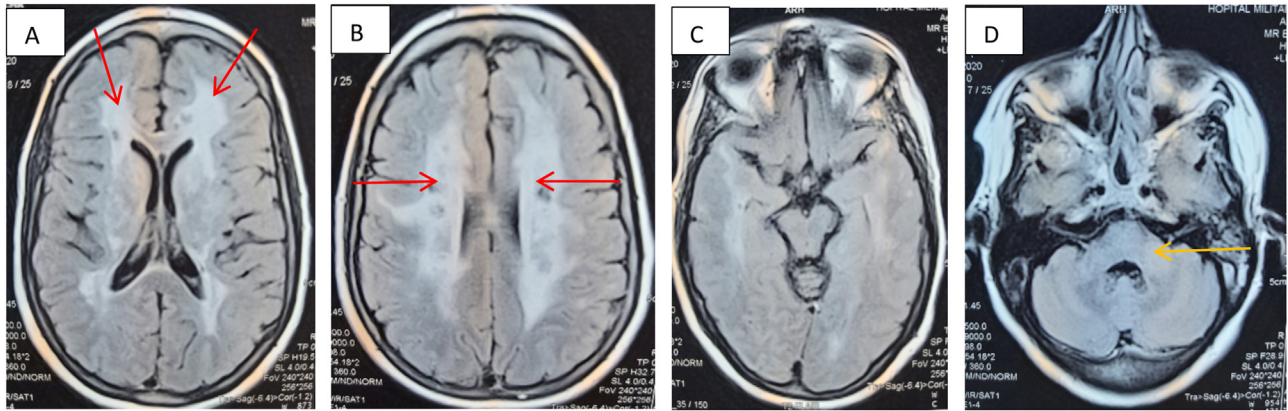


Fig. 6 – Brain MRI, FLAIR weighted images, showing multiple confluent hyperintense lesions located in the temporal lobes, centrum semi-ovale, left middle cerebellar peduncles and also the deep grey matter (thalamus and lenticular nuclei).

A CT of the chest was performed and showed subpleural ground glass opacities associated with interlobular reticular opacities forming a bilateral crazy paving aspect of Covid-19 pneumonia. The result of the nasal swab RT-PCR was positive. The brain MRI revealed multiple confluent hyperintense lesions on T2 and FLAIR weighted images located in the temporal lobes, centrum semi-ovale, left middle cerebellar peduncles (brachium pontis) and also the deep grey matter (thalamus and lenticular nuclei) (Fig. 6). The CSF analysis were normal with clear and colorless fluid, normal protein level, 0.36 g/L (normal range: 0.15–0.60 g/L) and glucose level, 0.59 g/L (normal range: 0.54–0.72 g/L), 4 white blood cells, and no germs detected. Immunoelectrophoresis of serum and CSF revealed no oligoclonal bands. The rest of the laboratory test was normal (CBC, CRP, serum biochemistry, urea, creatinine).

The patient received a 3-day course of intravenous methylprednisolone (1 g/day) followed by oral prednisone 1 mg/kg/j during 6 weeks tapered gradually. A progressive improvement of the symptomatology was noticed and the neurological examination after 3 months showed a moderate

left spastic hemiparesis with a left cerebellar syndrome. The last MRI of the brain showed some persistent signal anomalies in both white and grey matter and as well as in the left middle cerebellar peduncles (Fig. 7).

3. Discussion

Covid-19 infection has a rich repertoire of clinical manifestations to its clinical picture. Both central and peripheral neurological manifestations are among the most commonly encountered symptoms [1,2]. The Covid-19 virus is a neurotropic virus and several mechanisms underlie neurologic involvement, including hyperinflammation, hypercoagulability, and direct viral lesioning of neurons. In ADEM, an immune-mediated mechanism results in demyelination of CNS [3]. A number of myelin autoantigens such as oligodendrocyte glycoprotein, myelin basic protein, and proteolipid protein share antigenic properties with infectious agents such as the Covid-19 virus. This molecular mimicry leads to cross

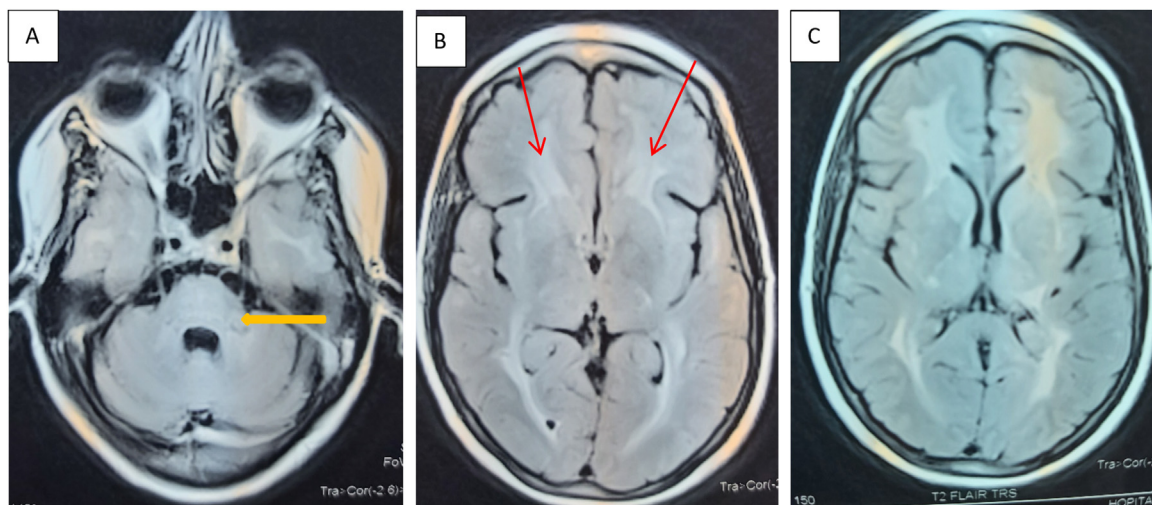


Fig. 7 – Brain MRI, FLAIR weighted images, showed some persistent hyperintense lesions in both white and grey matter (B, red arrows) as well as in the left middle cerebellar peduncle (A, yellow arrow).

reactions when the body synthesizes antibodies against foreign pathogens [2-4].

Our clinical cases involve three adults, two males and a female, who presented with ADEM after Covid-19 infection. The clinical manifestations in our patients were suggestive of encephalopathy with diffuse neurological impairment [5]. Patients presented with central vestibular system syndrome, upper motor neuron involvement, movement disorder, sensory deficit, cerebellar signs and impairment of consciousness. The constellation of these manifestations in each patient was suggestive of multifocal impairment that, given the context of Covid-19 infection, the clinical picture was sufficient to make us suspect the diagnosis of ADEM [6,7]. Patients presented with neurologic symptoms after an initial clinical picture dominated by respiratory symptoms ranging from benign flu-like symptoms to the more severe respiratory distress [8,9]. These respiratory symptoms were suggestive of Covid-19 infection and tests were performed accordingly. Based on the present literature, no clinical picture is specific of Covid-associated ADEM [10,11].

Typical MRI signs of ADEM include multiple hyperintense bilateral, asymmetric patchy lesions with poorly marginated borders on T2-weighted and fluid-attenuate inversion recovery images. The topography of these lesions includes the subcortical and central gray matter, the cortical gray-white matter junction, thalami, basal ganglia, cerebellum and brainstem [12,13]. Our patients presented diffuse demyelinating sub cortical lesions typically involving several regions in a bilateral asymmetric distribution. In addition to the above, we noted cerebellar and brainstem involvement in patients, without spinal cord lesions. Also, there was involvement of subcortical gray matter involvement. The involvement of gray matter in ADEM is a helpful distinguishing factor to exclude the diagnosis of multiple sclerosis. Also, the absence periventricular ovoid lesions and Dawson fingers on the corpus callosum should steer away the diagnosis from multiple sclerosis [14,15]. Contrast enhancement was observed in one of our patients. The same patient also had hemorrhagic lesions on MRI. Hemorrhagic lesions have been reported in Covid-associated ADEM [5]. It is possible that with the emergence of new data, more and more Covid-associated ADEM radiological specificities will be identified. A peculiar finding in Covid-associated ADEM was radial linear perivascular enhancement, typically seen in glial fibrillary acidic protein (GFAP) astrocytoma [8].

Spinal MRI in all three of our patients were normal. Laboratory workup should systematically exclude an infectious origin. An inflammatory cerebrospinal fluid profile has been noted in ADEM cases but it is generally mild and negative for presence of pathogens [5,8,9]. Other tests performed in our patients were in line with the clinical context. Case N 1 underwent an electromyography (EMG) with disclosed polyradiculopathy of lower limbs. In literature, peripheral nervous system involvement has been associated with ADEM [5]. Case N 3 presented with altered inflammatory markers on labs. This patient had an initial neurological presentation including altered consciousness with a more severe preceding respiratory clinical picture. One patient underwent stereotaxic brain biopsy. Biopsy in ADEM is not necessary for diagnosis. However, it might become necessary in pseudotumoral

presentations in order to exclude differential diagnosis such as other demyelinating disorders, tumor or abscess. Typically, biopsy shows same-age perivenous inflammation and demyelination of the CNS [10]. Inflammatory infiltration is lymphocytic and macrophagic. Pathology in our patient showed parenchymal inflammatory and infiltration with congestion.

Treatment is necessary to reduce morbidity and mortality of ADEM. It is both symptomatic and etiologic. Symptomatic measures include nursing and correct positioning in bed, prevention of seizures and correction of metabolic derangements susceptible of worsening the prognosis. High-dose intravenous corticosteroids are the first-line of treatment. All our patients were placed on high-dose intravenous corticosteroids, 1 g/day. The duration is between 3 to 5 days. Intravenous treatment is followed by oral taper over 4 to 6 weeks. Alternatively, intravenous immunoglobulins could be used in cases of nonresponse to steroids. In fact, a simultaneous administration of high-dose intravenous corticosteroids and intravenous immunoglobulins is possible. In cases of nonresponse, plasma exchange may be considered [1,11].

Outcome of treatment in patients with ADEM is generally favorable. However, in Covid-associated ADEM, prognosis seems poor with few complete recoveries, some deaths and the majority recovering incompletely [5]. Mortality seems relatively higher in adult patients than in pediatric patients. Other prognostic factors include form of disease, hospitalization in intensive care unit for consciousness impairment or respiratory distress. Acute hemorrhagic leucoencephalopathy is a controversial form of ADEM with hemorrhagic features on brain imaging and more severe pathologic findings on biopsy. This form is particularly characterized by high mortality [12-14]. Case N 2 presented with hemorrhagic lesions on brain MRI and died. A similar case was reported in the Paterson et al. series with non-response to IV corticosteroid. The patient required decompressive craniectomy and survived [5]. In ADEM occurring after SARS-CoV-2 infection, it is important to point out that the mortality due ADEM is intricated with the higher mortality due to Covid-19. Therefore, Covid-19 infection may be considered as worsening prognostic factors of Covid-19-associated ADEM. Radiological features, especially extension of lesions and brainstem involvement, are also important prognostic factors [12]. The presence of sequelae following initial attack may come in the form of persistent motor symptoms as well as cognitive impairment [15]. Transformation into a multiphasic ADEM or to another demyelinating disease is also a possibility yet to be reported in Covid-associated ADEM [6].

4. Conclusion

Covid-19-associated ADEM is an emerging phenomenon due to Covid-19 infections and vaccination. The disease follows a monophasic course but could leave sequelae or it may potentially recur or even evolve into another demyelinating disease. It is important to identify clinical signs suggestive of the diagnosis in patients treated for Covid-19. Differential diagnoses must be excluded on brain MRI, spinal tap and appropriate labs. Treatment is essentially immunomodulatory and supportive.

Disclosure of interest

The authors declare that they have no competing interest.

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