Case report

Neurological disorders in COVID-19: a case of Acute Disseminated Encephalomyelitis in an adult patient

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Abstract. Different neurological complications associated with the severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection have been widely documented. Acute disseminated encephalomyelitis (ADEM) is a rare immune-mediated demyelinating disorder, described within the spectrum of neurological manifestations of COVID-19. Herein, we describe a case of adult-ADEM presenting with diplopia and slowly progressive ataxia developed one month after SARS-CoV-2 infection. Brain magnetic resonance imaging (MRI) revealed acute multifocal demyelinating lesions throughout the brain. Other possible etiologies have been ruled out. After treatment with high-dose steroids, we observed a progressive clinical and radiological improvement. A 4-months follow-up showed complete clinical recovery. Although extremely rare, ADEM could be associated to SARS-CoV-2 infection and should be considered in the differential diagnosis. Early recognition of this COVID-19 neurological complication, even in the absence of pulmonary involvement, is important to start a prompt immune-modulatory treatment and, consequently, ensure a good outcome. (www.actabiomedica.it)

Key words: COVID-19, ADEM, inflammatory demyelinating lesions

Introduction

Several COVID-19-related neurological disorders have been reported, including anosmia, ageusia, consciousness alterations, status epilepticus, meningitis, encephalitis, Guillain-Barré syndrome and stroke (1-4).

The spectrum of acute neurological dysfunctions may depend to direct viral invasion, para-infectious complications, neurological manifestations of systemic diseases or co-incident neurological diseases (1).

Herein, we describe a case of acute disseminated encephalomyelitis post-COVID-19 infection.

Case report

A Caucasian 58-year-old man was admitted to the Emergency Department for slowly progressive ataxia and episodes of transient vertical diplopia started one month before and progressively worsened.

During medical interview, the patient referred that two months before, he suffered for diffuse weakness, cough and progressive olfactory and gustatory dysfunction. COVID-19 infection with mild symptoms was confirmed by means of polymerase chain reaction (PCR) assay and it resolved spontaneously within two weeks.

Neurological examination showed ataxic gait with tendency to left deviation, left sided dysmetria and mild left hemiparesis. Deep tendon reflexes were brisk with Babinski sign on the left. Neither alteration of ocular motility nor spontaneous nystagmus were seen. He was admitted to our Neurological Unit and underwent a complete diagnostic work-up.

Brain computed tomography (CT) was unremarkable, blood sample (white cells count, C-reactive protein level, metabolic panel, urine studies, electrolytes, thyroid hormones) was normal.

A first brain Magnetic Resonance Imaging (MRI) performed at day 3 demonstrated multiple T2 and FLAIR hyperintense lesions with surrounding edema, predominantly localized in the deep and periventricular white matter of frontoparietal and occipital lobes bilaterally, with involvement of corpus callosum, cerebellum and brainstem. Most of them showed restricted diffusion on Diffusion-Weighted Imaging (DWI) sequences and different patterns of gadolinium enhancement (Figure 1).

The MRI spectroscopy revealed a marked reduction of N-Acetyl Aspartate (NAA) and an increase in Choline (Cho) within regions corresponding to areas of high signal intensity on T2-weighted imaging.

A) FLAIR hyperintensity involved predominantly right midbrain and cerebral peduncle, periventricular white matter of frontal, temporal and occipital lobes with extension to the splenium of corpus callosum.

B) Contrast-enhanced axial T1-weighted MRI images showed multiple patchy and cloudy asymmetric enhanced lesions, in particular in right midbrain and left temporal-occipital regions. The left frontal lesion presented an evident gadolinium-enhancing rim.

SARS-CoV-2 PCR from a nasopharyngeal swab was negative and evaluation of SARS-CoV-2 serology assays revealed the presence of anti-SARS-CoV-2 IgG antibodies.

Cerebro-spinal fluid (CSF) examination showed a slight increase in protein content (508 mg/L, normal value 150-450 mg/L) with normal leukocyte count and negative oligoclonal band (OCB); bacterial culture, glucose level and neurological viral PCR panel (Adenovirus, Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus, Varicella Zoster virus) were all

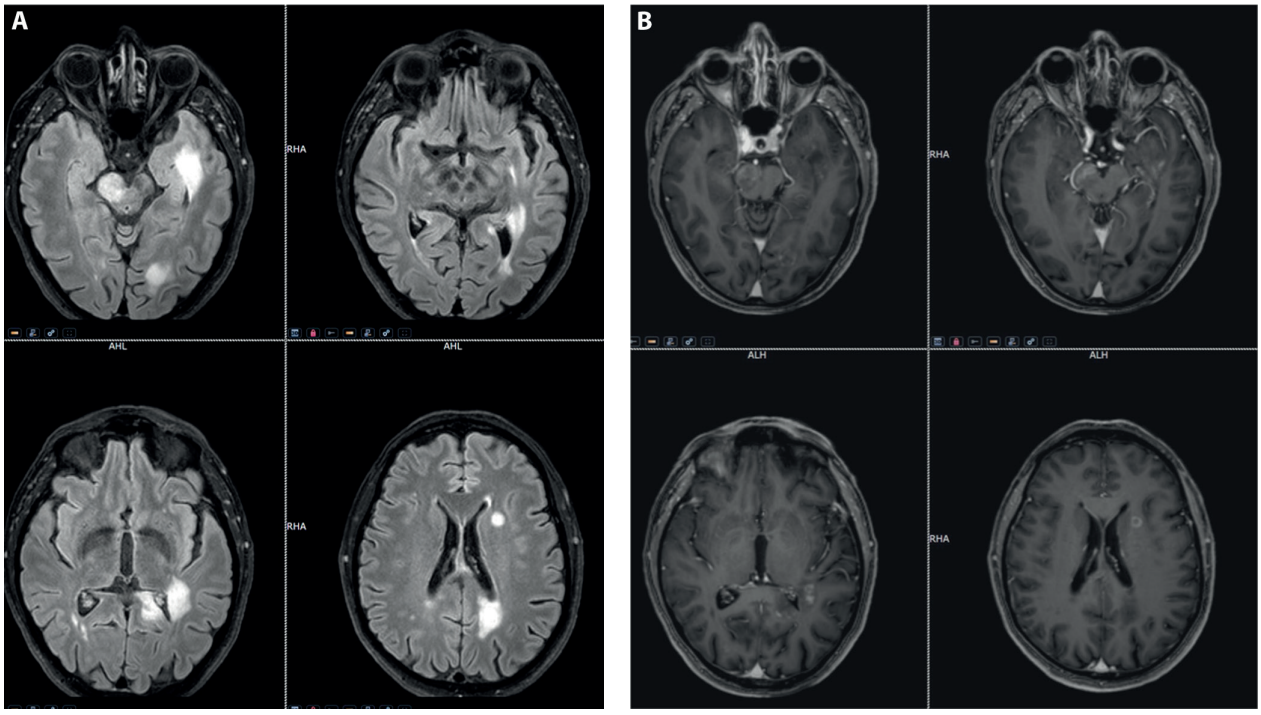

Figure 1. First brain Magnetic Resonance Imaging (MRI) findings.

unremarkable. CSF cytology revealed the presence of white blood cells (5.0/μL), but it was negative for malignancy. CSF cytokine profile showed an increase of IL-8; SARS-CoV-2 was not detected by qualitative PCR.

Serum antibodies including anti-myelin oligodendrocyte glycoprotein (anti-MOG), anti-thyroid peroxidase, anti-nuclear, anti-double-stranded DNA, anti-neutrophil cytoplasmic, anti-HIV, anti-Treponema Pallidum, onconeural and targeting neuronal surface antigens were all negative. A screening for immune-mediated encephalitis, including antibodies against NMDAR, LGI1, CASPR2, $GABA_AR$, $GABA_BR$ and AMPA was negative.

Chest-abdomen CT was unremarkable.

A second brain MRI was performed on day 16, showing a slight reduction in edema and contrast enhancement of the white matter lesions, with increased signal abnormalities on DWI; minimal leptomeningeal enhancement was also noted.

Acute disseminated encephalomyelitis (ADEM) was suspected and intravenous high-dose of methylprednisolone (1 gr daily for 5 days), tapered with oral prednisone, were administered with a slight clinical improvement.

One month later, at discharge, the patient still presented an ataxic gate and a mild left hemiparesis. Walking was nevertheless possible with monolateral support.

Two months later, a follow-up MRI demonstrated a partial improvement with reduction in the size of lesions within cerebral hemispheres, cerebellum and brainstem. New lesions were not identified, and no pathological meningeal enhancement was noted. At neurological assessment, ataxia and left hemiparesis remarkably improved.

Another brain MRI, performed four months later, showed further reduction in size and extent of FLAIR hyperintense areas within the periventricular and subcortical white matter, without enhancement (Figure 2).

Significant reduction in size and FLAIR hyperintensity of all previous cerebral lesions.

At this time, neurological symptoms and signs were completely relieved.

Brain MRI performed one year later demonstrated a further improvement of previous findings, without new lesions.

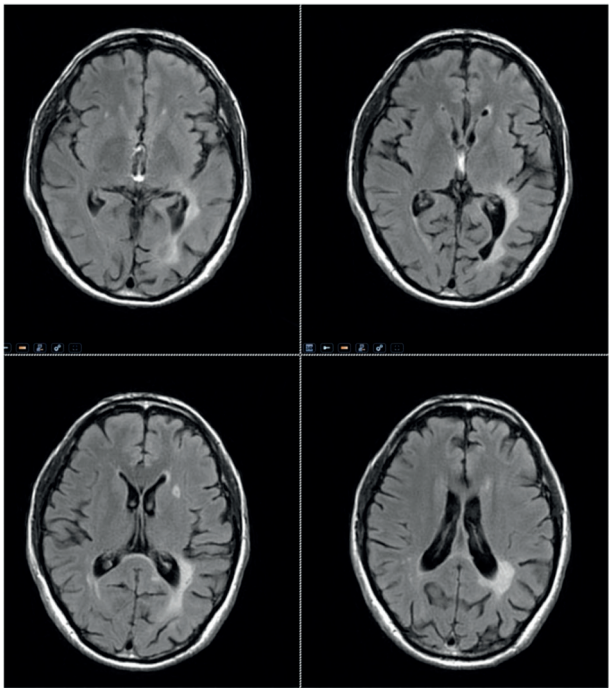

Figure 2. Brain MRI at 4 months-follow-up.

Discussion

Herein, we describe a case of probable adult-ADEM developed one month after mild SARS-CoV-2 infection. Other possible etiologies have been ruled out, particularly infection diseases of the central nervous system and malignancy. After treatment with high-dose steroids, we observed a progressive clinical and radiological improvement, with complete clinical recovery after 4 months.

Although extremely rare, ADEM could be associated to SARS-CoV-2 infection and should be considered in the differential diagnosis (5-7). Early recognition of this COVID-19 neurological complication, even in the absence of pulmonary involvement, is important to start a prompt immune-modulatory treatment and, consequently, ensure a good outcome.

ADEM is a monophasic and multifocal immune-mediated demyelinating disorder of the central nervous system (CNS), affecting multiple areas of the brain white matter, rarely the gray matter and the spinal cord, often resolving after treatment in a 3-months period (8,9).

ADEM mainly affects children under 10 years, more commonly males, with an incidence of 0.3-0.6 per 100,000 per year (8-10).

In adults, it is rare and usually appears between the ages of 30 and 50, with equal sex preponderance.

ADEM generally arises 2 to 40 days after viral or bacterial infection or, more rarely, after vaccinations (11).

The most frequent infections involved are viral and include: rubella, mumps, measles, varicella, mononucleosis and influenza. Moreover, infections by herpes simplex virus, cytomegalovirus, hepatitis A virus, enterovirus and coronavirus have been associated with ADEM.

Other pathogens anecdotally involved in ADEM are: borrelia burgdorferi, toxoplasma gondii, cryptococcus neoformans, haemophilus influenzae type B, leptospira sp, streptococcus pyogenes, plasmodium falciparum, mycoplasma pneumoniae, rickettsia sp. and campilobacter jejuni (11).

According to literature, ADEM can be considered a transient autoimmune disease following T cell-mediated cross-activation and response against myelin proteins, through a mechanism of molecular mimicry, although exact pathogenesis of ADEM remains still unclear (11).

It is characterized by an acute onset of encephalopathy associated with multiple neurological deficits, often preceded by prodromal symptoms, such as fever, headache, nausea, vomiting and weakness.

About neurological manifestations, a prominent clinical feature is encephalopathy, defined as a change in behavior and/or consciousness, although its absence should not rule out the diagnosis of ADEM. Other neurological signs include multifocal or focal deficits, such as ataxia, hemiparesis, diplopia, aphasia, dystonia or choreiform movements, seizures and speech impairment. Multiple cranial nerve involvement has been described, especially of the optic nerve. Finally, spinal cord syndrome may be present (8, 9, 11).

The diagnosis of ADEM is based on the combination of clinical features and brain MRI findings. However, others diseases must be excluded before a definite diagnosis could be made. Differential diagnosis of ADEM includes multiple sclerosis (MS), viral encephalitis, posterior reversible encephalopathy syndrome (PRES), toxic encephalopathy, progressive multifocal leukoencephalopathy (PML), adult onset leukodystrophies and cerebral autosomal dominant arteriopathy (CADASIL) (9).

In 2007, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) proposed clinical and radiological diagnostic criteria for pediatric ADEM, updated in 2013 (12,13).

The ADEM criteria proposed by IPMSSG require:

1. polyfocal clinical CNS event with presumed inflammatory demyelinating cause;
2. encephalopathy (alteration in consciousness or behavior) that cannot be explained by fever or systemic illness;
3. brain MRI abnormalities consistent with demyelination during the acute (3 months) phase;
4. no new clinical or MRI findings after three months from the clinical onset.

Typical MRI findings include: 1) large (>1-2 cm) and diffuse lesions involving predominantly cerebral white matter; 2) rare white matter lesion resulting hypointense in T1 weighed imagines; 3) possible deep gray matter lesions.

Despite the lack of conclusive evidence, immunotherapy is considered standard of care and may contribute to faster recovery and improved outcome. Particularly, high-dose corticosteroids are currently considered as first-line therapy, while intravenous immunoglobulin (IVIG) treatment has been used in corticosteroid-resistant patients.

Finally, in patients with a severe fulminant disease or unresponsive to corticosteroids and IVIG, plasma exchange is recommended.

In pediatric population, full recovery has been reported for most patients. Long time sequelae are not frequent. The majority of patients have a resolution, both complete and partial, of MRI lesions.

In our case, the presence of acute and diffuse involvement of CNS, mainly affecting the cerebral white matter, the onset four weeks after a viral infection due to SARS-CoV2 and the absence of other possible causes suggested a probable association (2).

Moreover, the monophasic course, the good response to steroid therapy and the complete clinical recovery supported the hypothesis of ADEM.

A recent systematic review of the literature reported 34 cases of ADEM after Covid-19 infection and 14 cases of acute hemorrhagic leukoencephalitis (AHLE), a subtype of ADEM (14). Nine patients were children (19%), 31 patients (64%) had a poor outcome at discharge and 5 (10%) patients died in hospital.

Finally, ADEM has also been described following vaccination for preventing Covid-19 infection (15).

Compared to classic ADEM, SARS-CoV-2 ADEM shows some differences: first of all, symptoms of ADEM meanly start after a longer period from the beginning of the infectious disease. Furthermore, patients are older and present a more severe outcome than classical ADEM. Finally, regarding MRI imaging, SARS-Cov-2-ADEM more frequently shows, as in our case, periventricular white matter and corpus callosum involvement, and less frequently affected the deep gray matter.

Conclusions

This case of probable ADEM, occurred after mild symptoms of SARS-CoV-2 infection, broads the descriptions reported in literature.

Prompt diagnosis and effective therapeutic support might have contributed to a favorable outcome. Conversely, in case of diagnostic delay, some patients might develop neurological sequelae.

Although rare, ADEM can be associated to SARS-COV-2 infection and should be considered in the differential diagnosis.

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Consent Statement: The case report was written after getting the patient informed consent, according to our hospital policy to obtain patients data for clinical practice and research.

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