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Case report

Abrupt bilateral blindness as a rare post-acute demyelinating consequence of COVID-19

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could prompt various neurological complications. Abrupt visual disturbance was reported as a rare severe manifestation of post-coronavirus disease 2019 (COVID-19). Autoimmune conditions were assumed to have an undeniable role in creation of such circumstances. This report presents a 69-year-old woman with sudden bilateral blindness three weeks after recovering from a SARS-CoV-2 infection. Demyelination due to COVID-19-related autoimmune disorder of the central nervous system (CRAD-C) was considered to be the etiology of her bilateral blindness. Due to her progressive demyelination, immunosuppressive treatments were administered, which resulted in stabilizing post-COVID-19 demyelinating lesions. Accordingly, in the case of COVID-19-related neurological deficits, especially the acute and progressive symptoms, there should be great consideration of autoimmune response to prevent serious complications; hence early diagnosis, treatment, and long-term assessment of patients are necessitated.

1. Introduction

Many reports and studies indicated that coronavirus disease 2019 (COVID-19) is associated with neurologic complications [1]. Olfactory involvement, headache, and impaired consciousness were more commonly described [1]. Although rare, visual loss was described as an uncommon complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [2–6]. The major causes of visual loss in the acute or post-acute phase of the SARS-CoV-2 infection are cerebrovascular attacks [2], encephalitis [3], post reversible encephalitis syndrome (PRES) [4], and herpes simplex viruses (HSV) reactivation-related retinal necrosis [5]. Likewise, demyelination was a recognized mechanism linked to SARS-CoV-2 blindness in patients with COVID-19-related autoimmune disorder of the central nervous system (CRAD-C) [6,7].

Here we report a case of a 69-year-old woman with post-acute bilateral blindness three weeks after recovering from SARS-CoV-2 infection, who has enlarging demyelinating lesions on brain magnetic resonance imaging (MRI).

2. Case presentation

A 69-year-old woman with a past medical history of hypothyroidism was admitted to our hospital with abrupt bilateral vision loss. Three weeks before the onset of symptoms, she was diagnosed with SARS-CoV-2 infection (due to fever, weakness, shortness of breath, and positive polymerase chain reaction (PCR) test for SARS-CoV-2 infection). She was treated with remdesivir and dexamethasone for five days. Headache, weakness, paresthesia, or other neurological complaints were not present at the time of admission to our clinic. She did not have any past medical history of prior SARS-CoV-2 infection.

On physical examination, there was complete bilateral blindness and fixed-mydriatic pupils with absent light reflex. In a fundoscopic examination, bilateral papilledema with splinter hemorrhages was reported. Due to her blindness, visual evoked potential (VEP) could not be performed. Other neurological examinations were normal.

First MRI revealed T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense lesions in deep white matter of the right occipital lobe and left side of the pons (Fig. 1). These lesions showed mild restriction on diffusion-weighted imaging (DWI) and ring enhancement on post gadolinium T1-weighted images (Fig. 1). Comprehensive paraclinical studies, including magnetic resonance venography (MRV),

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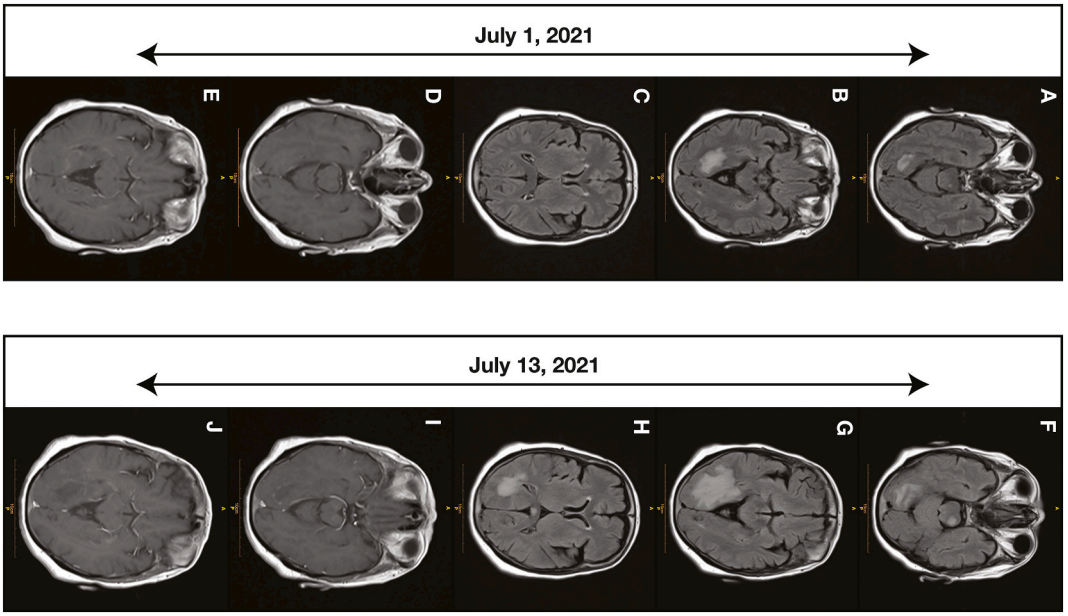

Fig. 1. Brain magnetic resonance imaging (MRI) over two weeks of treatment. Two weeks after the first presentation, fluid-attenuated inversion recovery (FLAIR) MR images determined progression of hyperintense lesions in (A and F) deep white matter of the left side of the pones and (B and G) right occipital lobe, accompanied by the formation of a new lesion in (C and H) corpus callosum. In T1 post-contrast MR images, progression of lesions in (D and I) pones and (E and J) occipital lobe along with ring enhancement were detected.

Table 1
Serum investigation.

Blood investigations	Case	NL	Vasculitis panel	Case	NL	Paraneoplastic panel	Case
Hb	13.4	12.3–15.3	**ANA**	0.01	<10	**Titin Ab IgG**	Negative
HCT	38.5	35.9–44.6	**Anti-dsDNA**	2.78	<10	**Zic 4 Ab IgG**	Negative
RBC	$4.4*10^6$	$4.1*10^6$-$5.1*10^6$	**C-ANCA**	0.1	<12	**GAD65 Ab IgG**	Negative
WBC	6500	4400–11,000	**P-ANCA**	0.1	<12	**Tr(DNER) Ab IgG**	Negative
PLT	197,000	150,000–450,000	**Anti-Cardiolipin IgM**	1.3	<12	**SOX1 Ab IgG**	Negative
PBS*	Normal		**Anti-Cardiolipin IgG**	9.8	<12	**Amphiphysin Ab IgG**	Negative
ESR*	9	0–33	**Lupus Anticoagulant**	Negative	28–40	**CRMP-5(CV2Ab) IgG**	Negative
CRP*	5	0–6	**Anti-Phospholipid IgM**	0.5	<12	**PNMA2(Ma-2/Ta) Ab IgG**	Negative
ACE*	8	8–65	**Anti-Phospholipid IgG**	1.4	<12	**Ri Ab IgG**	Negative
LDH	384	0–530	**Beta-2 glycoprotein Ab**	1.6	<15	**YO Ab IgG**	Negative
Alpha-fetoprotein	0.5	<5.8				**Hu Ab IgG**	Negative
***B*-hCG**	Negative					**Recoverin Ab IgG**	Negative
Immunofixation serum	Negative						

* ACE: Angiotensin converting enzyme, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PBS: Peripheral blood smear.

Table 2
Cerebrospinal fluid analysis.

CSF analysis	Case	Paraneoplastic panel	Case
Color	Colorless	**Titin Ab IgG**	Negative
RBC	3–5	**Zic 4 Ab IgG**	Negative
WBC	0	**GAD65 Ab IgG**	Negative
Glucose	61 mg/dl	**Tr(DNER) Ab IgG**	Negative
Protein	51 mg/dl	**SOX1 Ab IgG**	Negative
LDH	40	**Amphiphysin Ab IgG**	Negative
Gram smear	Negative	**CRMP-5(CV2Ab) IgG**	Negative
CSF culture	Negative	**PNMA2(Ma-2/Ta) Ab IgG**	Negative
CSF cytology	Negative	**Ri Ab IgG**	Negative
OCB*	Negative	**YO Ab IgG**	Negative
IgG index	Negative	**Hu Ab IgG**	Negative
		Recoverin Ab IgG	Negative

* OCB: Oligoclonal band.

magnetic resonance angiography (MRA) of the brain, MRI of cervical cord as well as color doppler ultrasound of carotid and vertebral arteries, could not reveal any pathological findings. All laboratory studies, including panel tests for autoimmune vasculitis, were normal (Table 1).

The patient underwent a diagnostic lumbar puncture which determined a normal opening pressure along with a normal biochemical and cytological profile of cerebrospinal fluid (CSF) (Table 2). Serologic antibody assays for toxoplasmosis and HSV 1 & 2 were reported negative. Cell-based antibody assays for anti-aquaporin-4 antibody (AQP4-Ab) and antibody against myelin oligodendrocyte glycoprotein (anti-MOG-Ab) were also negative.

We began a high-dose methylprednisolone course (1000 mg/day) treatment for three days. Since the patient did not respond to this treatment and a new symptom in the form of right hemiparesthesia was added to her complaints, a new brain and orbital MRI were performed, which determined some progression in both T2 and FLAIR MR images as well as a new lesion in the splenium of corpus callosum (Fig. 1). Orbital MRI was normal. Computed tomography (CT) scan of thorax, abdomen, and pelvic did not reveal any primary tumor. Magnetic resonance spectroscopy (MRS) of cerebral lesions confirmed the demyelinating nature of these lesions. For evaluation of the underlying malignancy source, routine tumor screening tests and paraneoplastic panel from serum (Table 1) and CSF (Table 2) were performed and reported negative for the patient.

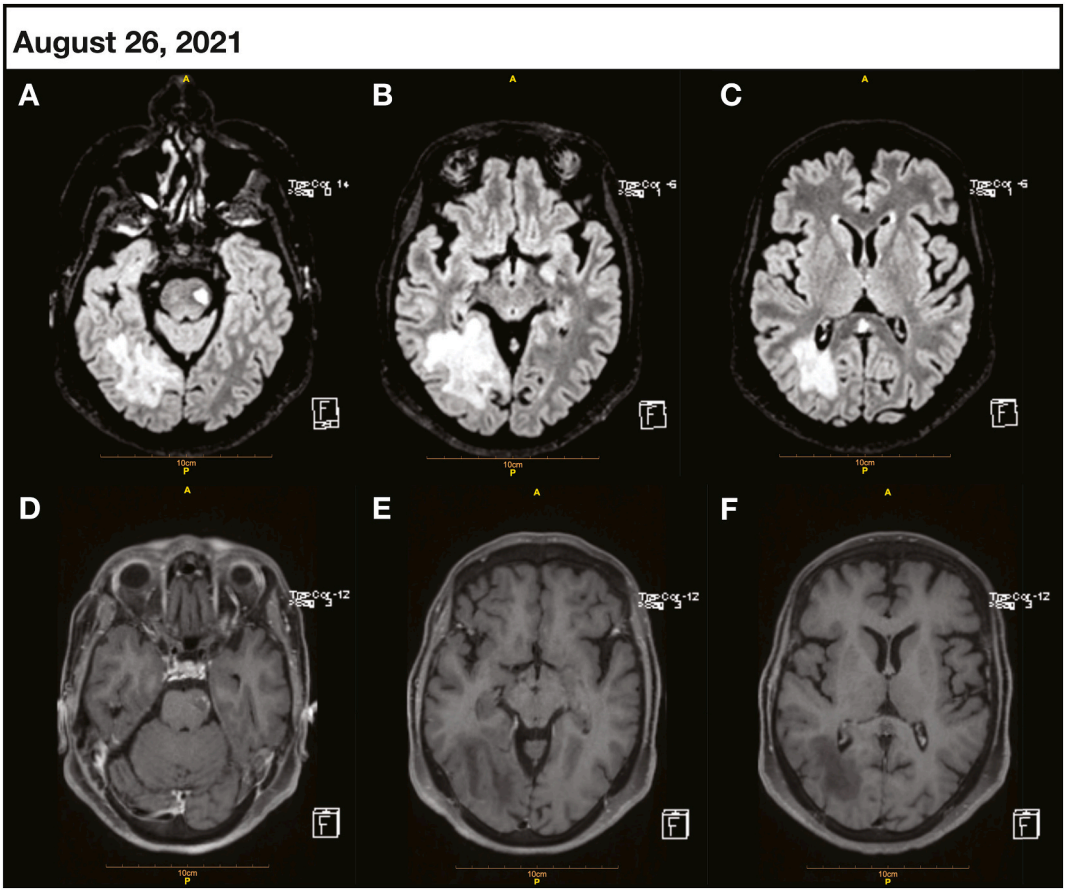

Fig. 2. Follow-up brain MRI. One month after treatment, (A) pones, (B) right occipital lobe, and (C) corpus callosum FLAIR MR images determined no changes in previously reported lesions. Also, (D, E, and F) no enhancement was detected in T1 post-contrast MR images.

Given no benefit from treatment and progression of previously reported lesions that were accompanied by the formation of a new lesion, therapeutic plasma exchange (TPE) for seven days (1–1.5 x of total plasma volume on each day) was initiated. Since the patient did not respond to TPE, induction therapy with cyclophosphamide was started to control the progressive demyelination process. According to the protocol recommended in previous studies, cyclophosphamide was administered as an initial induction dose of 1000 mg daily for two days and then 1000 mg monthly for three months until the patient developed leukopenia $<2000/mm^3$ [8].

One month later, at her follow-up examination, there was an improvement in her paresthesia without any changes in her visual acuity. There were not any new neurological complications. A new control MRI was taken and did not determine any activity (enhancing, new, or enlarging T2/FLAIR lesion) (Fig. 2). Due to the fact that the patient's condition was clinically and radiologically stable, rituximab was given as maintenance treatment at a dose of two 1000 mg, two weeks apart and will be continued every six months upon results of CD19 flow-cytometry assessment.

3. Discussion

Recent evidence determined molecular mimicry and immune system hyper-stimulation response as two main mechanisms related to CRAD-C [9]. Immune-mediated mechanisms in the pathogenesis of CNS demyelinating disorders and immune responses to SARS-CoV-2 have some common inflammatory pathways which were predominantly considered to be the etiology for CRAD-C [10]. Previous studies showed that dysregulation of proinflammatory cytokines like IL-6, IL-17 is evident in COVID-19 and CNS-demyelinating conditions [10,11]. These conditions include a variety of demyelinating disorders ranging from encephalitis, transverse myelitis, and Guillain–Barre syndrome, as the most common to the infrequent reports; like multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and MOG antibody disease (MOGAD) which could be due to para- or post-infectious complications of COVID-19 [10].

Various autoimmune CNS complications, including acute disseminated encephalomyelitis (ADEM), MS, and NMOSD, were increasingly reported in patients with SARS-CoV-2 infection [12,13]. We present a rare case of post-COVID-19 complication manifested as CNS-demyelinating disorder with sudden bilateral blindness. According to clinical and MRI findings, this was a disseminated and progressive demyelination. Although ADEM was placed as the first differential diagnosis, MRI lesions were asymmetric and progressive without obvious peripheral edema [12], which were not classic for ADEM. The clinical course consisted of at least two clinical relapses, which is not typical in patients with ADEM [14]. A similar pattern of post-acute demyelinating disorder after viral infection was previously reported by Mabrouki et al. [6]. Our patient's clinical and radiologic characteristics would mostly be considered a CRAD-C presentation that needed an effective immunosuppressive treatment.

The progressive demyelination in the presented case did not respond to corticosteroids and TPE. Intensive immunosuppressive therapy with cyclophosphamide was reported as an induction therapy in controlling rapidly progressive demyelinating lesions [15]. Therefore, according to the patient's condition, we chose cyclophosphamide to control the rapid progression in the acute phase of the disease. Given that cyclophosphamide-induced immune suppression is temporary and the side effects of long-term use of this drug are serious [8], we started rituximab as a maintenance treatment.

Post-COVID-19 neurological syndrome (PCNS) is reported to take place following CRAD [13,16]. PCNS refers to the long-term neurological complications of COVID-19 infection [16]. The onset of these complications could be slow, like in neurodegenerative disorders including Alzheimer's disease or rapidly progressive [13,16] such as the one in the presented case. Considering the rapid nature of this condition which could result in disseminated demyelinating lesions, it seems that prevention of seriously progressive COVID-19-related demyelination is only feasible through early evaluation of CRAD-C. Therefore, timely immunosuppressive treatment is necessitated to prevent severe complications.

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Author contributions

A.M, I.A, S.N, and V.S contributed to the conception and design of the research. A.M wrote the first draft of the manuscript. I.A, S.N, and V.S revised the manuscript. All the authors have read and approved the final version.

Compliance with ethics guidelines

Written informed consent has been obtained from the patient. This study was approved by the Iranian national committee for ethics in biomedical research (Approval ID: IR.MUI.MED.REC.1400.451) and performed in accordance with the Helsinki Declaration of 1964, and its later amendment.

Declaration of Competing Interest

The authors declare no competing interests.

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