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CASE REPORT

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COVID-19 and optic neuritis: a series of three cases and a critical review

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Abstract

Background The novel coronavirus disease (COVID-19) has claimed innumerable lives globally since its onset and several extrapulmonary manifestations of the disease have been reported in association with COVID-19. Although optic neuropathy has been previously linked to a variety of infections, neuro-ophthalmological associations of SARS-CoV-2 have been sparsely reported till date. Our aim was to report the clinical profile and outcome of patients diagnosed with parainfectious/postinfectious optic neuritis (ON) associated with COVID-19.

Case presentation In this case series, we have discussed the clinical presentation, laboratory parameters and outcome in a series of three patients of ON associated with COVID-19 and also compared those findings against existing literature. Among the three patients, two patients (Case 1, 3) were incidentally diagnosed with COVID-19 during the course of hospital admission and contributed to a parainfectious association with ON, while one patient (Case 2) had an antecedent history of COVID-19 as evidenced by her antibody titers thus contributing to a postinfectious association. Notably, all these patients were asymptomatic or had mild manifestations of COVID-19 and all of them tested negative for myelin oligodendrocyte glycoprotein (MOG) antibodies. They were treated accordingly and their visual outcomes were noted in follow-up.

Conclusion ON with or without MOG seropositivity, probably attributed to molecular mimicry has surfaced up considerably in association with COVID-19. This article provides a comprehensive overview of clinical presentation and outcome of ON associated with parainfectious/postinfectious COVID-19 in three cases and a critical analysis of existing literature.

Keywords COVID-19, Optic neuritis, Parainfectious, Postinfectious, Molecular mimicry, MOG

Background

Since its outbreak, the coronavirus disease 2019 (COVID-19) pandemic has wreaked havoc worldwide, irrespective of geo-politico-social boundaries. It has been a source of perplexity to infectious disease experts worldwide, that the causative agent, severe acute respiratory syndrome corona virus (SARS-CoV2), albeit being a primarily respiratory pathogen, causes myriad manifestations, of which neurological involvement is common [1]. Several pathophysiological mechanisms have been proposed in an attempt to explain the neurological involvement of COVID-19 namely, direct neurotoxicity of the virus due to its affinity to angiotensin-converting enzyme 2 (ACE2) receptors, disruption of blood–brain subsequent to a cytokine storm, hyperinflammatory syndrome leading to immune-mediated damage, molecular mimicry, prothrombotic state [2]. However, neuro-ophthalmological manifestation of this disease has been sparsely reported in literature. A variety of infections have been linked to optic neuropathy with variable visual impairment ranging from a spectrum of papillitis to retrobulbar

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optic neuritis [3]. Direct involvement of the optic nerve or immune-mediated inflammation, degeneration, or vascular mechanisms may be contributory in infectious optic neuropathy. Recent literature has also linked SARS-CoV-2 and optic neuritis (ON), in presence or absence of primary central nervous system demyelinating lesion namely, myelin oligodendrocyte glycoprotein (MOG) antibody disease, which may open new avenues of interconnection between COVID-19 and demyelination [4]. The authors hereby reported a series of three cases of postinfectious ON associated with COVID-19, admitted in Bangur Institute of Neurosciences, IPGMER & SSKM Hospital, India, between 2021 and 2022 and also narrated a brief review on this neuro-ophthalmological complication among the protean manifestations of this disease.

This series describes the clinico-demographic profiles, possible pathogenesis and outcomes of three patients diagnosed with ON associated with COVID-19. Written informed consent (from patients or their kin) was obtained. After obtaining detailed history, the patients underwent meticulous clinical examination and routine laboratory workup followed by pertinent investigations. Given the rarity of this association of ON with COVID-19, we further reviewed the literature on PubMed and Medline databases using Medical Subject Headings (MeSH) terms "Optic neuritis" or "ON" and "COVID-19" or "SARS-Cov2".

Case presentation

Case 1

An 8-month-old female child born out of a non-consanguineous marriage with uneventful birth history and normal developmental milestones developed a sudden onset loss of parallelism of both eyes and subsequently her mother noted that the child was also unable to follow objects with her eyes. The child did not have any history of fever, diarrhea or vaccination prior to onset of this event. However, her mother was diagnosed with COVID-19 and was managed in home isolation with mild symptoms two weeks back. On examination, the child had an esotropia of left eye with poor visual fixation in both eyes, optokinetic nystagmus was not elicitable and fundoscopy revealed bilateral disc edema; no long tract signs were present. A magnetic resonance imaging (MRI) [Magnetom Avanto, Siemens Healthineers, India] of orbit revealed a T2 hyperintensity of the intraorbital part of both optic nerves (Fig. 1) with post-contrast enhancement of the optic sheath suggestive of perineuritis. Brain MRI and spinal cord screen were unremarkable. A visual evoked potential (VEP) [Neuropack X1 MEB-2300, Nihon Kohden, Japan] study revealed bilateral retino-optic pathway dysfunction. Cerebrospinal fluid analysis (CSF) revealed mild lymphocytic pleocytosis (cell count-8/cumm) with elevated protein (62 mg/dl) and normal glucose (56 mg/dl), oligoclonal bands as well were not detected and IgG index was normal. Serum biomarkers of neuromyelitis optica (NMO) spectrum disorder (anti-aquaporin 4 antibodies) and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies were also negative. Considering the close contact of the child with her mother, who was diagnosed with COVID-19, a SARS CoV-2 RTPCR was done to the child, which turned out to be negative, however anti-SARS CoV-2 S was elevated with high titer (142.90; positive > 0.80 U/ml). She was initiated on injectable pulse methylprednisolone therapy (15 mg/kg/day for 3 days) followed by a tapering dose of oral prednisolone initiated at 1 mg/kg. She had a gradual uneventful recovery and was followed up after a month with better visual fixation on examination and resolving disc edema on fundoscopy.

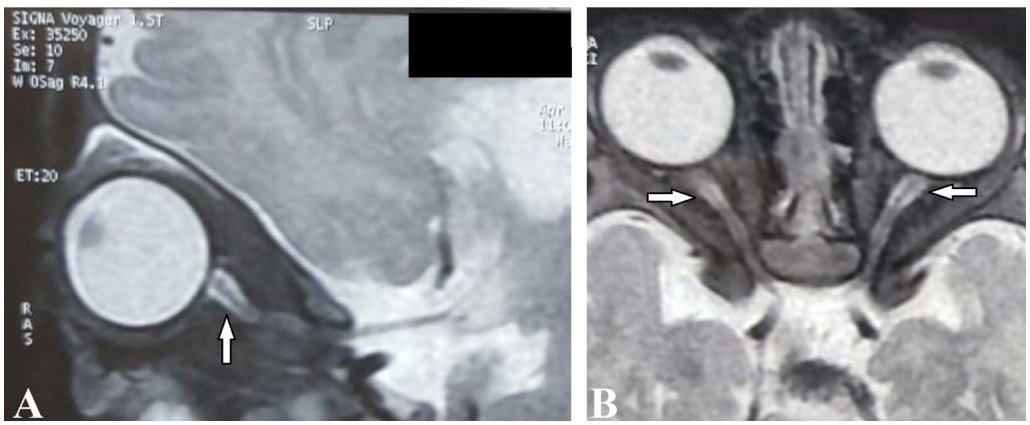

Fig. 1 MRI orbit sagittal section showing T2 hyperintensity of intraorbital portion of right optic nerve (**A**) and axial section showing T2 hyperintensities of both optic nerves (**B**)

Case 2

A 21-year-old female with no known comorbidities presented with a progressive dimness of vision in her right eye associated with periorbital pain on eye movements, without any other local eye symptoms. She also experienced color desaturation with a sharp diminution in visual acuity of right eye within a week. She has not experienced a prior attack similar to this episode and had no motor/sensory deficit, bowel/bladder dysfunction. Fifteen days prior to onset of this illness, she was diagnosed with COVID-19, which was managed conservatively in home isolation. On examination, she had a visual acuity of 3/60 in her right eye with a relative afferent pupillary defect (RAPD) and fundoscopy revealed disc edema in the right eye. Brain imaging was non-contributory and orbital imaging revealed a post-contrast enhancement of the intraorbital part of right optic nerve (Fig. 2). Visual evoked potential was suggestive of a retino-optic pathway dysfunction in the right eye and a prolonged p100 latency in the left eye. Perimetry was suggestive of a central scotoma in the right eye. An acellular CSF sample with normal protein level (38 mg/dl) was obtained. No oligoclonal bands were detected in CSF and serum biomarkers of NMO (anti-aquaporin 4 antibodies) and anti-MOG antibodies turned out to be negative. Causes of secondary demyelination were negated with suitable investigations. Her serum anti-SARS-Cov-2 S was elevated (356; positive > 0.8 U/ml). She was diagnosed with a clinically isolated syndrome (CIS) and initiated on intravenous methylprednisolone for 3 days followed by a tapering dose of oral prednisolone (1 mg/kg/day), after which she had a partial recovery and was followed up after 3 weeks with a visual acuity of 6/60 in her right eye.

Case 3

A 16-year-old male presented with a sudden onset color desaturation followed by blurring of vision in his left eye which progressed to an extent of near blindness within a week, not associated with any local eye symptoms or any other focal neurodeficit. He was febrile and had mild dry cough which resolved spontaneously. On examination he had only perception of light in right eye, relative afferent pupillary defect (RAPD) and disc edema. Post-contrast enhancement of optic nerve was seen on imaging (Fig. 3) and VEP of the left eye revealed no waveform. RTPCR for SARS CoV-2 from a nasopharyngeal and oropharyngeal swab turned out to be positive. Studying of CSF revealed lymphocytic pleocytosis (10 cells/cumm) with normal protein (45 mg/dl) and RTPCR for SARS CoV-2 was negative. Supportive investigations negated other probable primary/secondary demyelinating etiology. He experienced mild subjective improvement after a course of oral steroids following pulse methylprednisolone therapy and achieved a vision of 6/60 in left eye after 4 weeks of follow-up.

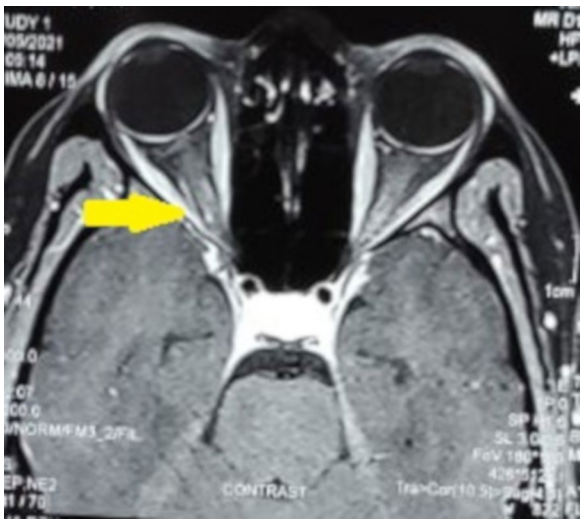

Fig. 2 MRI orbit post-contrast T1 axial-weighted image showing contrast enhancement of sheath of right optic nerve suggestive of perineuritis

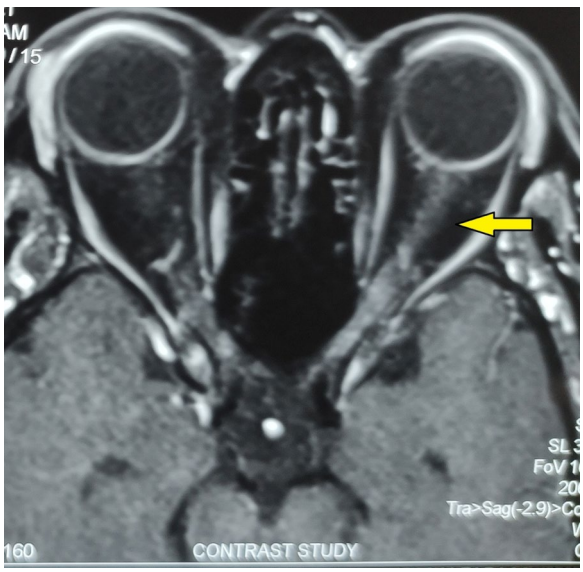

Fig. 3 MRI orbit post-contrast T1 axial-weighted image showing contrast enhancement of sheath of left optic nerve suggestive of perineuritis

Conclusion

ON is an immune-mediated, predominantly unilateral, inflammatory, demyelinating condition that causes acute to subacute loss of visual acuity, progressing over hours to days. It is the presenting feature in 25% of patients of multiple sclerosis (MS) and occurs in around 70% of them at some stage of illness [5]. Systemic T cell activation leads to the release of cytokines and other inflammatory agents which in turn lead to Bcell activation against myelin basic protein leading to immune-mediated demyelination, although the target antigens are yet to be identified [6]. The association of ON ranges from several infectious etiology (viral, bacterial, parasitic and fungal) to primary demyelination (MS, NMO spectrum disorders, MOGAD) as well as secondary demyelinating etiologies (sarcoidosis, SLE, Sjogren, PAN, Behcet, vasculitis).

This series illustrates the association of ON with parainfectious/postinfectious COVID-19. In the first case, the child had a history of close contact with a confirmed case and was incidentally detected to be RT-PCR positive for SARS-CoV-2. Similarly, the third case was incidentally detected to be positive, in absence of any history of contact or pulmonary manifestations. These two patients were categorized as mild COVID-19 disease and recovered spontaneously with conservative management. In the second case, the patient had an antecedent history of mild COVID-19 following which she developed a postinfectious ON. All three cases were managed with pulse methylprednisolone followed by tapering doses of oral steroids, with gradual improvement of vision on regular follow-up. Henceforth, we report two cases of parainfectious (Case 1, 3) and one case of postinfectious (Case2) ON; however, the pathophysiology in these two instances may be varied and still remains elusive. A descriptive comparison between our cases and previously reported cases is depicted in Table 1.

The neurotropism of SARS-CoV-2 virus is poorly elucidated; access of the virus to central nervous system through the olfactory bulb, crossing the blood–brain barrier following viremia, transport via infected leukocytes are probable mechanisms [13]. Parainfectious/postinfectious demyelination has been described in various neurological complications like Guillain-Barré syndrome, acute transverse myelitis associated with COVID-19 [14, 15]. Although a positive SARS-CoV-2 RT-PCR in CSF serves as concrete evidence of direct neuroinvasion of the virus, negative results do not rule out the possibility of CNS infection, as PCR testing for SARS-CoV-2 in CSF is yet to be validated in clinical settings. Moreover, in cases of non-arteritic ischemic optic neuropathies (NAION), thromboinflammatory potential of SARS-CoV-2 may lead to endotheliitis or microthrombosis as well as papillophlebitis leading to capillary ischemia and occlusion resulting in optic atrophy [16]. Molecular mimicry in which viral antigens may induce an immune response against self-proteins, may be a plausible mechanism of demyelination in COVID-19 associated ON.

The potential of SARS-CoV-2 for autoantibody production has been illustrated in manifestation of myelin oligodendrocyte glycoprotein antibody disease (MOGAD) following COVID-19 infection. MOG-IgG antibodies are produced against MOG, expressed on oligodendrocytes serving as a cellular receptor which also stabilizes microtubule stability. MOGAD is mediated by T cells and complement fixation, once these antibodies gain access to the central nervous system by disruption of blood–brain barrier [17]. Parainfectious/postinfectious demyelination linked to a prodromal viral illness is well established, possible pathogenesis involve molecular mimicry mediated by an immune response against myelin triggered by viral antigens [18]. SARS-CoV-2 is endowed with the ability to ignite a profound immune response in the patients involving a cascade of cytokines and inflammatory mediators. Considering the established link between a viral prodrome and MOGAD, SARS-CoV-2 infection followed by MOG antibody mediated demyelination has been reported in a considerable number of cases. Inability to identify this immunological basis for vision loss may lead to a delayed diagnosis of the underlying COVID-19 disease, which may be asymptomatic. ON is the most common ocular event with a mean onset of 10.8 days post-vaccination, linked to nine different vaccines as per a review on adverse ocular events from 2010 to 2020 [19]. Sporadic reports of post-vaccination ON have surfaced up in the literature, though causation or coincidence is yet to be established [20]. COVID-19 has baffled the world with its pleomorphic manifestations, of which neurological diseases bear no exception. ON with or without MOG IgG seropositivity has been considerably reported in association with COVID-19. Although molecular mimicry remains as the probable mechanism of immune-mediated event in this context, the direct role of virus mediated inflammation still remains elusive as retinitis, uveitis have been simultaneously reported with ON in few cases. This series provides a comprehensive overview of clinical presentation and outcome of ON associated with parainfectious/postinfectious COVID-19 disease, compared to existing literature. The knowledge of this association may prompt further research to decipher the exact pathogenesis, expand the spectrum of CNS demyelination and help in developing precise therapeutic targets.

Table 1 Descriptive comparison of reports showing association of optic neuritis and COVID-19; MOG-myelin oligodendrocyte glycoprotein, ON-optic neuritis, RTPCR-reverse transcriptase polymerase chain reaction, HM-hand movement, PL-perception of light, PR-projection of rays, N/A-not assessable

Study	Population and site	Visual impairment	Therapy received	Degree of visual recovery	Status of COVID-19 infection	MOG antibody
Sawalha et al. [7]	Male, 44 years; bilateral ON	Right-6/60 Left-6/9	I/V Methylprednisolone (1gm × 5 days)	Complete recovery in left eye with partial restoration of vision in right eye	RTPCR positive 2 weeks prior to optic neuritis; mild respiratory symptoms managed in home isolation	Detected
Zhou et al. [8]	Male, 26 years; Bilateral sequential ON and TM	Right- HM, Left -6/75	I/V Methylprednisolone (1gm × 5 days) followed by oral prednisolone taper	6/9 vision in both eyes 3 weeks later	RTPCR positive at the time of clinical presentation; mildly symptomatic for COVID-19	Detected
Žorić et al. [9]	Male, 63 years; Right ON	Right- 6/190	I/V Methylprednisolone (1gm × 5 days) followed by oral prednisolone taper over two weeks	6/7.5 vision in right eye 3 weeks later	RTPCR negative serology (IgM, IgG) positive for COVID-19, 4 weeks prior to ON; moderate COVID-19 disease	Detected
François 2021 et al. [10]	Female, late 50 s; Right ON with retinitis	Right-HM	Oral and topical corticosteroids	HM in right eye after 45 days	RTPCR positive at time of clinical presentation; mild COVID-19 disease	Not mentioned
Benito-Pascual 2020 et al. [11]	Female, 50 years; left ON with panuveitis	Left- 6/60	Oral corticosteroids taper	6/12 in left eye	RTPCR positive at time of clinical presentation; moderate COVID-19 disease	Not mentioned
Rodríguez-Rodríguez MS et al. [12]	Female, 55 years; left ON	Left- 6/60	I/V Methylprednisolone × 5 days followed by oral prednisolone taper	6/120 in left eye after 4 weeks	RTPCR positive at time of clinical presentation; asymptomatic COVID-19	Not mentioned
Present series	1. Female, 8 months; bilateral ON 2. Female, 21 years; right ON 3. Male, 16 years; left ON	1. N/A 2. Right-3/60 3. Left- PL/PR	1.I/V Methylprednisolone (15 mg/kg) × 3 days followed by oral prednisolone taper 2.I/V Methylprednisolone (1gm/kg) × 3 days followed by oral prednisolone taper 3.I/V Methylprednisolone (1gm/kg) × 3 days followed by oral prednisolone taper	1. N/A 2. Right-6/60 after 3 weeks 3. Left-6/60 after 4 weeks	1.RTPCR positive at time of clinical presentation; asymptomatic COVID-19 2.RTPCR positive 15 days prior to ON; Mild COVID-19 disease 3. RTPCR positive at time of clinical presentation; asymptomatic COVID-19 disease	1. Negative 2. Negative 3. Negative

Abbreviations

ON	Optic neuritis
MOG	Myelin oligodendrocyte glycoprotein
SARS-CoV2	Severe acute respiratory syndrome corona virus
ACE2	Angiotensin-converting enzyme 2
MeSH	Medical subject headings
MRI	Magnetic resonance imaging
VEP	Visual evoked potential
CSF	Cerebrospinal fluid
NMO	Neuromyelitis optica
RTPCR	Reverse transcriptase polymerase chain reaction
MS	Multiple sclerosis

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Author contributions
UC, JC contributed to conception, initial drafting of manuscript. AKD, AM, AP, BKR, GG conducted critical revision of content and final approval of manuscript. All authors have testified that all persons designated as authors qualify for authorship and have checked the article for plagiarism. All authors had substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of the data; drafting the work or revising it critically for important intellectual content, and final approval of the version to be published. All agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The approval of institutional ethics committee was waived.

Consent for publication
Informed documented written consent was obtained from the patients or from their legal guardian.

Competing interests
The authors declare no competing interests.

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