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COVID 19- threat to vision: A case series

Dr Somya Singhal[1]*, Dr Dharmendra Jhavar[1], Dr Archana Verma[2] , Dr V.P.Pandey[3], Dr Abhishek Nagar[4] , Dr Shubham Upadhyay[5]

[1]*, 4, 5 Resident Medical Officer, [1] Professor, 2Associate Professor, , 3Professor and Head
Department of Medicine, M.G.M. medical college and M.Y.H. group of hospital, Indore, Madhya Pradesh ,India

***Corresponding Author:**
Dr Somya Singhal
Resident Medical Officer, Department of Medicine, M.G.M. medical college and M.Y.H. group of hospital Indore, Madhya Pradesh

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ABSTRACT

Background: Idiopathic Intracranial Hypertension (IIH) is a neurologic disorder characterized by raised intracranial pressure (ICP) without a known aetiology. A demyelinating inflammation of the optic nerve defines optic neuritis. Permanent residual deficits in visual acuity, colour vision and visual field are common in both the diseases if untreated. A sudden presentation of COVID 19 patients with visual complaints prompted us to evaluate the causes and led to diagnosis of COVID 19 related neuro-ophthalmic manifestations.

Methodology: This is a retrospective case series with collection of data from three COVID 19 patients who presented with visual complaints to MYH Group of Hospitals, a dedicated COVID19 centre with 1200 bed occupancy.

Results: All the patients in this case series were female of child bearing age group and had BMI either in the range of overweight or obesity. COVID 19 antibody test was negative in both the patients presented with IIH. The patient with retrobulbar optic neuritis had significantly high level of COVID 19 antibody which might be responsible for triggering autoimmunity or demyelination in this patient. All of these patients responded very well to conventional treatment.

Conclusion: The sudden rise in COVID 19 cases with visual complaints coinciding with peak of COVID-19 pandemic points to an epidemiological cause and effect relationship between the two. Two cases of Idiopathic Intracranial Hypertension and one of retrobulbar optic neuritis in one month during COVID-19 pandemic raises a possibility of COVID-19 triggered mechanism.

Keywords: NIL

INTRODUCTION

We are learning that neuro-ophthalmic manifestations can be part of the SARS-CoV-2 infection or can be precipitated by the infection [1]. Viral infections have also been considered as a possible trigger for demyelinating disease in brain since a long time in multiple diseases like Progressive Multifocal Leukoencephalopathy (PML) and Subacute Sclerosing Panencephalitis (SSPE) [2].

Optic neuritis (ON) is defined as demyelinating inflammation of the optic nerve. Most common cause associated with optic neuritis are multiple sclerosis (MS) or Neuromyelitis Optica (NMO), but optic neuritis can occur in isolation. Occasionally, optic neuritis can also be a result of an infectious process involving the orbits or paranasal sinuses or occur in the course of a systemic viral infection [3].

Idiopathic Intracranial Hypertension (IIH) is characterized by increased CSF pressure inside the skull. Elevated CSF pressure can lead to two problems, severe headache and visual loss. Permanent visual loss or blindness may result as a result of this untreated elevated CSF pressure [4].idiopathic intracranial hypertension is diagnosed by **modified Dandy Criteria [5].**

The incidence of Idiopathic Intracranial Hypertension in the general population is thought to be about 1 per 100,000[6] and of new-onset optic neuritis is 4-5 cases per 100,000 persons [7]. Usually we come across 1-2 patients of Idiopathic Intracranial Hypertension per year and 2-3 patients of retro bulbar optic neuritis amongst 4500- 5000 new patients in our tertiary care neurology services per year. A sudden rise in the incidence of COVID 19 cases with these above mentioned diagnosis was noted this year during the month of September 2020, the period coinciding with the occurrence of corona virus (COVID-19) pandemic in the Indore city, India.

Case 1:

On 14september2020, a 27-year-old female health care worker involved actively in COVID care (BMI-24.7 kg/mm2), without comorbidities, presented to the emergency room with fever and dyspnoea since one day. She also had a complaint of a headache that had started two days before presentation. Patient did not have any history of periorbital swelling or redness of eyes, trauma and pain in eyes on movement. Patient did not have any significant past history, social history or addiction history. Patient denied for any use of tetracycline, vitamin A derivatives and oral contraceptives. During hospitalization on day 3, the headache worsened with multiple episodes of vomiting and she noticed a severe diminution of vision that patient was unable to see a person clearly at around 6 feet distance and unable to read sign boards on road.

She was fully oriented, without focal neurological deficits. On ophthalmological examination it was revealed that patient had bilateral ill sustained pupillary light reaction, bilateral visual acuity of 6/60, and normal colour vision with full range of extraocular movements.

On bilateral fundoscopy by Ophthalmologist, patient showed blurring of nasal disc margin characterizing early papilledema (figure 1A, 1B).

Figure 1:

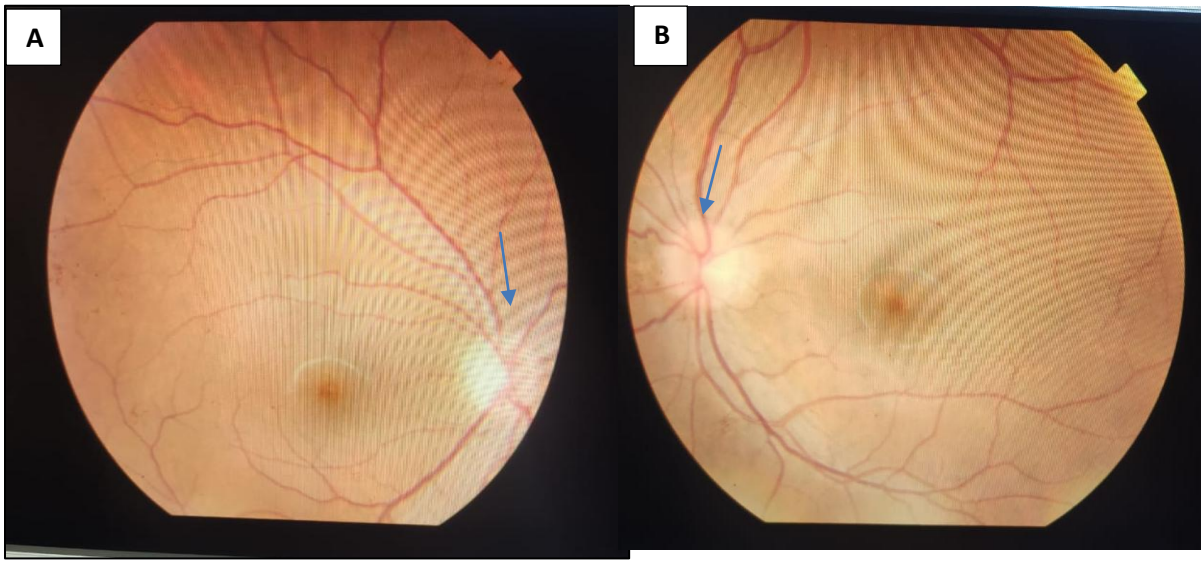

Figure 1 A and 1B showing fundus photographs of patient with optic disc swelling with burring and elevation of nasal disc margin (arrow) suggesting early papilledema

On biochemical evaluation patient showed a normal hemogram with normal renal function test, liver function test, thyroid profile, HBA1c, fibrinogen, D dimer, CRP and ESR. Patient was non-reactive for HIV, Hepatitis B, Hepatitis C and VDRL.

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Perimetry and Visual Evoked Potential was found to be normal with no visual field defect or increased latency respectively.

An Magnetic Resonance Imaging Brain, Orbit With Venogram was performed which showed signs of intracranial hypertension characterized by bilateral optic nerve sheath distension in intraorbital segment of optic nerve with normal brain parenchyma and Venogram (figure 1C).

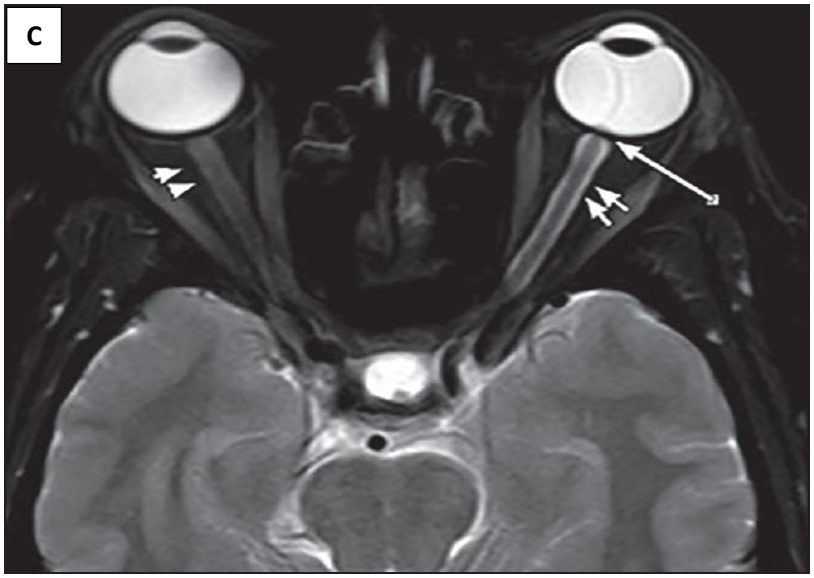

Figure 1C showing T2 axial magnetic resonance imaging scan of orbit shows distension of the optic nerve sheath in intraorbital segment of optic nerve bilaterally

Lumbar puncture was performed which showed increased CSF opening pressure of 26 cm H2O (normal-below 20 cmH_2o) by standard CSF manometry. The cerebrospinal fluid analysis was having low protein content (7 mg/dl) with rest of the normal findings which also favoured intracranial hypertension.

Real-time reverse-transcription polymerase chain reaction testing of a nasopharyngeal swab confirmed SARS-Cov-2 infection. Chest computed tomography was completely normal with no changes of pneumonitis or ground glass opacities. Anti-Nuclear Antibody, c-ANCA and p-ANCA was also negative in this patient. Serum Parathyroid Hormone level and serum calcium levels were within normal range.

The final diagnosis based on clinical, laboratory, and imaging findings was Idiopathic Intracranial Hypertension (IIH). The patient was treated with intravenous mannitol for 3 days and supportive measures for COVID 19 infection during 5 days course of hospitalisation. Patient was discharged with acetazolamide 250mg twice daily for 1 month. Patient was followed after discharge and showed visual acuity improvement to 6/6p with disappearance of headache and vomiting at the end of one month. This patient on follow up was tested for COVID19 antibody by chemiluminescent micro particle immune assay which revealed negative result for the same.

Case 2:

Within One week of encountering first case, A previously healthy 30 -year-old female (body-mass index 27·2 kg/m²) presented to our hospital with 5 days history of fever, myalgia, dyspnoea, headache, vomiting and one day history of diminution of vision. Because of diminished vision patient was unable to read letters on board kept at around 3 meter distance. Patient was not having any rashes over body with no history of cough, periorbital swelling, redness or pain in eyes, altered level of sensorium or seizures. There was no significant past medical history, social, addiction history or history of drugs intake.

On Initial clinical assessment patient was fully conscious and oriented without focal neurological deficit. Patient revealed bilateral visual acuity of 6/36 with normal colour vision, bilateral normal pupillary

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light reaction, full range of extraocular movements and without any focal neurological deficit.

Dilated fundus examination revealed bilateral papilledema with nasal disc margins blurring (figure 2A, 2B).

Figure 2:

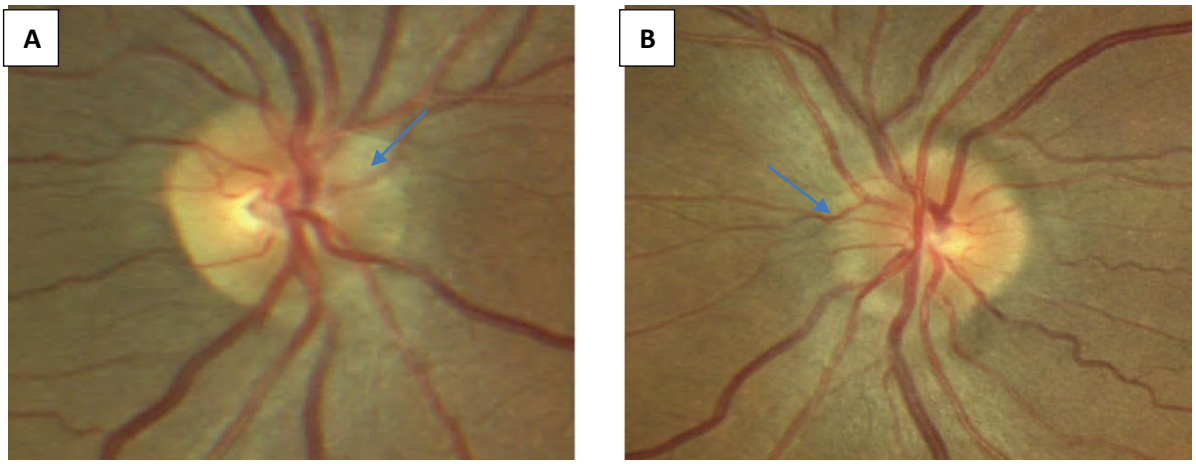

Figure 2 A and 2B showing fundus photographs of patient with optic disc swelling with burring of nasal disc margin (arrow) suggesting early papilledema

On initial laboratory assessment upon presentation showed normal WBC count, ESR, C-reactive protein, fibrinogen, D dimer, international normalised ratio and partial thromboplastin time. Nasopharyngeal sampling for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time PCR was positive. High resolution CT Chest showed normal lung parenchyma and interestitium.

Magnetic Resonance Imaging of the brain and magnetic resonance venogram was planned for evaluation of cause of diminished vision and this revealed abnormalities consistent with increased intracranial pressure characterized by prominent subarachnoid space around optic nerves, vertical tortuosity of the optic nerves, and superior compression of the hypophysis (figure 2C, 2D) with normal brain parenchyma and no focal lesions.

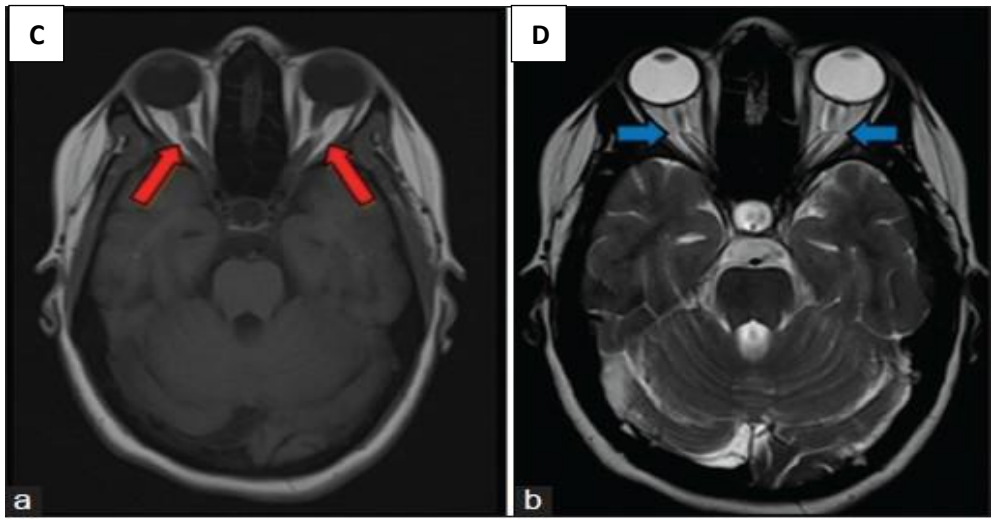

Figure 2C and 2D showing T1 and T2 Magnetic resonance imaging of brain with orbit axial section showing tortuosity of bilateral optic nerve (arrow)

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Lumbar puncture after admission to hospital revealed a CSF opening pressure of 27 cm H_20 by standard CSF manometry and low protein (14mg/dl) with other biochemical and microscopic analysis in normal range. Anti-Nuclear Antibody and ANCA was negative in this patient. Parathyroid Hormone level and serum calcium levels were normal.

On the basis of clinical, biochemical, radiological and lumbar puncture findings patient was finally diagnosed as idiopathic intracranial hypertension. Patient was given intra venous mannitol for 3 days and supportive treatment for COVID 19 infection for 7 days. Patient was discharged with Acetazolamide 250 mg twice daily. Patient showed a significant improvement with treatment and at the end of one month visual acuity improved to 6/9p with resolving papilledema in fundus.

On follow up this patient also showed negative result for COVID antibody test by chemiluminescent micro particle immune assay at the end of one month.

Case 3

Simultaneously, a 35 year female(BMI – 24.9 kg/mm2) presented to emergency room with complaint of sudden loss of vision in left eyes since one day with pain on movement of eye since one week. On further evaluation patient revealed history of fever, cough and myalgia two week back for which she took paracetamol and conservative management at home. There was no history of headache, vomiting, altered sensorium, seizures, tingling in any part of body, weakness in any limb, swelling around eyes, redness in eye or discharge from eye.

There was no past medical history of note, no history of trauma and unremarkable social and addiction history.

On clinical evaluation patient was conscious and fully oriented without focal neurological deficit. Patient revealed relative afferent pupillary defect, visual acuity as counting finger at 2 feet only and colour blindness in her left eye. Right eye was normal in ophthalmological evaluation. Her fundus examination was normal in both the eyes (figure 3A).

Figure 3:

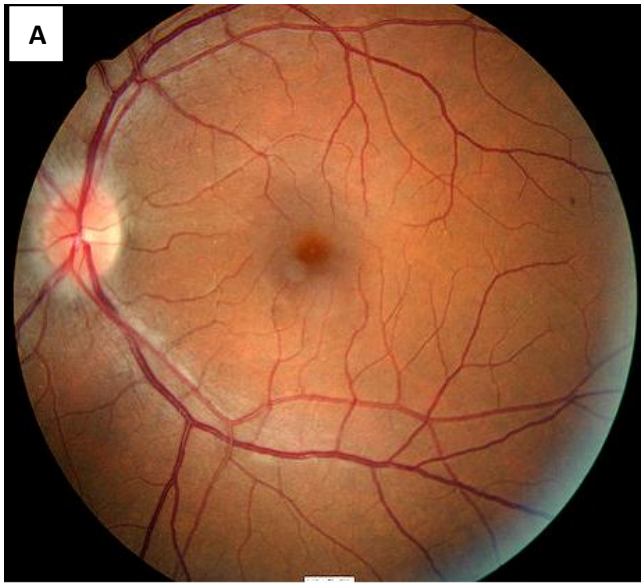

Figure 3A showing fundus photographs of patients with clear optic disc margins suggesting normal fundus

Visual evoked potential showed increased latency in left eye with loss of P100 response. Perimetry revealed left eye nasal visual field defect.

On biochemical evaluation patient showed raised CRP (12.1 mg/l) ,raised ESR (45mm/hr) , normal WBC, renal function test, liver function test, Fasting blood sugar, post prandial blood sugar, HBA1c, thyroid profile with normal Vitamin B12 level.

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Magnetic resonance scan of brain and orbit showed abnormalities consistent with retro bulbar optic neuritis characterised by intrasubstance T_2 flair hyper intense signal in left optic nerve with demyelinating lesions in bilateral fronto-parietal periventricular subcortical white matter with normal MRI spine (figure 3B).

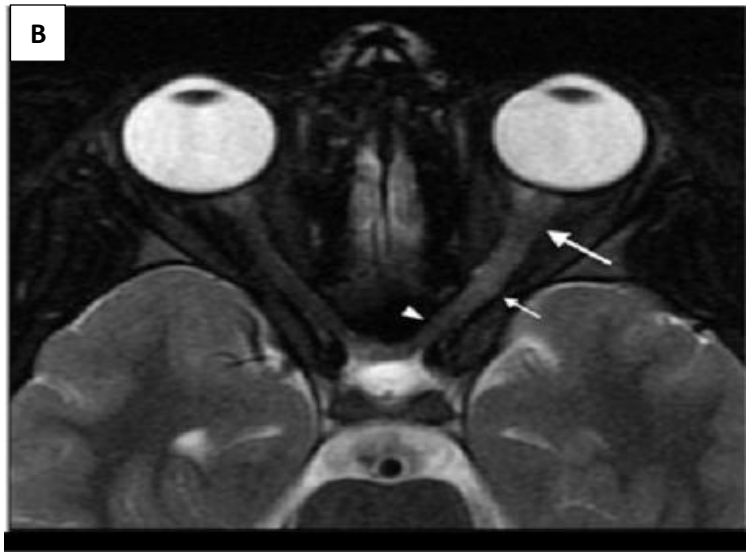

Figure 3 B showing T2 Magnetic resonance imaging of orbit axial section showing intrasubstance T_2 flair hyper intense signal in left optic nerve

Patient was reported negative for ANA, p-ANCA, c-ANCA, VDRL, HIV, Hepatitis B, Hepatitis C and Lyme antibody. Patient had normal serum calcium and ACE levels.

Patient CSF was negative for HSV PCR, aquaporin 4 antibody, oligo clonal band and anti MOG antibody. Nerve conduction study of all 4 limbs came out to be normal.

As there was history of fever 2 week back, Nasopharyngeal sampling for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time PCR was done which reported to be negative. Patient was tested for COVID antibody levels which showed a significantly raised level as 174.29mg/dl/. Patient was finally diagnosed with retrobulbar optic neuritis possibly of COVID 19 origin. Patient was treated with intra venous methylprednisolone 1g once daily for 5 days with supportive measures. Patient was discharged with tapering dose of oral steroids. Patient showed a significant improvement in visual acuity to 6/12 at the end of two weeks with colour vision returned back to normal.

Summary of these cases are shown in table 1.

Table -1: Salient features of patients presented to MYH group of Hospitals:

	Case 1	Case 2	Case 3
Age(year)	27	30	35
Gender	Female	Female	Female
BMI	24.5kg/mm2	27.2kg/mm2	24.9kg/mm2
Comorbidity	Nil	Nil	Nil
Presenting symptoms	Fever, Headache	Headache Vomiting	Pain in left eye on movement

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		vomiting Diminution of vision	Diminution of vision fever	Diminution of vision
Date of COVID19 positive(RT-PCR)		14.9.2020	21.09.2020	Negative by RT-PCR
Severity of Respiratory illness		Mild illness	Mild	Mild
HRCT chest		WNL	WNL	WNL
Date of onset of fever		12.9.2020	15.9.2020	4.9.2020
Date of onset of visual symptoms		16.9.2020	19.09.2020	20.09.2020
Ophthalmological findings	1.visual acuity	6/60 (bilateral eye)	6/36 (bilateral eye)	Counting finger at 1 feet (left eye)
	2.colour vision with Ishihara chart	WNL	WNL	Red green blindness
	3.anterior segment	NAD	NAD	NAD
	4.intraocular pressure	15mmhg	14mmhg	16mmhg
	4.pupillary reaction	Bilateral eye non sustained pupillary light reflex	Normal	Relative Afferent Pupillary Defect in left eye
	5.Extra Ocular Movement	Full range of movement	Full range of movement	Full range of movement
Fundus		Bilateral nasal disc margin blurred s/o Bilateral papilledema	Bilateral papilledema with blurring of nasal disc margin	Normal
Perimetry		WNL	WNL	Nasal field visual field defect
Visual Evoked Potential		WNL	WNL	Loss of P100 response and prolonged latency
MRI brain, orbit and venogram		Bilateral optic nerve sheath loosening with	Prominent subarachnoid space around	Intrasubstance T_2 flair hyper intense signal in left optic

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		normal magnetic resonance venogram.	optic nerves, vertical tortuosity of the optic nerves, and superior compression of the hypophysis with normal MR venogram.	nerve with demyelinating lesions in bilateral fronto-parietal periventricular subcortical white matter with normal MRI spine
CSF analysis	Manometry (CSF opening pressure)	27 cmh_20	26 cmh_20	15 cm h_20
	Routine and microscopy	Low protein level (7 mg/dl)	Low protein level (14mg/dl)	Raised protein level Negative for HSV PCR and oligo clonal bands
Other investigations		ANA,ANCA-negative PTH level , S. calcium – normal HIV ,Hepatitis B , Hepatitis C,VDRL – non reactive	ANA,ANCA-negative PTH level , S. calcium – normal HIV ,Hepatitis B , Hepatitis C, VDRL – non reactive	ANA,ANCA, -negative anti-aquaporin 4 antibody- negative anti MOG antibody –negative PTH level , S. calcium, thyroid profile, Vitamin B12 level - normal HIV ,Hepatitis B , Hepatitis C, Lyme Antibody, VDRL – non reactive
COVID19 antibody test by CMIA		Negative	Negative	174.29mg/dl
Diagnosis		Idiopathic Intracranial Hypertension	Idiopathic Intracranial Hypertension	Retrobulbar Optic Neuritis
Treatment		Mannitol, Acetazolamide 250 mg bid and supportive measures.	Mannitol, Acetazolamide 250 mg bid and supportive measures.	Methylprednisolone 1gram once daily for 5 days followed by oral tapering of steroids.
Outcome in visual acuity		6/6 partial	6/9 partial	6/12

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RESULTS

- All the patients in this case series were female of child bearing age group.
- All patients had BMI either in the range of overweight or obesity.
- All of these patients presented with significant visual problems and with mild respiratory involvement with COVID 19.
- COVID19 antibody test was negative in both of the patients presented with IIH.
- The patient with retrobulbar optic neuritis had significantly high level of COVID19 antibody which might be responsible for triggering autoimmunity or demyelination in this patient and response to methylprednisolone also favors the same.
- All of these patients responded very well to conventional treatment. High dose corticosteroid methylprednisolone 1 gram once daily for 5 days led to excellent result in patient with retrobulbar optic neuritis.

DISCUSSION

Idiopathic intracranial hypertension is one of the secondary headache disorder characterized by headaches and visual symptoms. It is most prevalent in obese women of childbearing age. However, many secondary causes exist, and it may affect children, men, and slim individuals [8]. Optic neuritis is an inflammatory condition of the optic nerve characterized by a sudden onset of unilateral visual loss, usually affecting young females [9].

In our study, patients with IIH showed a negative antibody response while antibody level was significantly higher in patient with retrobulbar optic neuritis. Total anti-bodies were determined by chemiluminescent micro particle immune assay, which is an automated, rapid and high throughput assay, objective and quantitative. Pie Wang et al showed that chemiluminescent micro particle immune assay has sensitivity (95.7 %) and specificity (98.7 %) of total antibodies against SARS-COV-2. Of the 141 COVID-19 patients, 135 patients showed positive antibodies against SARS-CoV-2. Six patients out of the 141 COVID-19 patients were found to be antibody negative, 4 of them were RT-PCR positive [10].

Viral infections had been known to induce autoimmunity and demyelination since a long time. Viral infections have also been found to be associated with rise in intracranial pressure but this kind of raised intracranial pressure is known as secondary intracranial hypertension to viral encephalitis. But COVID 19 infection has found to be associated with primary rise in intracranial tension without causing viral encephalitis. Fabio Noro presented first report of COVID-19 associated with isolated Idiopathic Intracranial Hypertension in May 2020[11]. A recent case report has also been published on idiopathic intracranial hypertension associated to Multisystem inflammatory syndrome in children (MIS-C), a recently reported paediatric syndrome associated with SARS-CoV-2 infection.[12]

Till now we did not come across about correlation of COVID 19 infection with retrobulbar optic neuritis. But if we focus on the coronavirus family, there is clear evidence of its neurotropic character as demyelinating disease has been previously reported with MERS and SARS-CoV-1. Recent studies have shown that the novel coronavirus appears to cross the blood-brain barrier and cause acute or delayed CNS demyelination or axonal damage. A variety of mechanisms have been postulated including virus-induced hypercoagulable or pro-inflammatory states, direct viral invasion of the CNS, and post-infectious immune-mediated processes [13]. SARS-CoV-2 virus has strong affinity toward human ACE-2 receptor. ACE-2 receptor is expressed in multiple tissue including glial cells and neurons. Thus, if virus once reach to central nervous system or peripheral nervous system neurons and glial cells are important targets [14]. However, data remains limited in terms of cases of CNS post-infectious demyelinating/inflammatory disease following COVID-19.

Conclusion:

This series conclude that sudden rise in cases with visual complaints in patients of COVID-19 at the peak of pandemic points to an epidemiological cause and effect relationship between the two. Two cases of Idiopathic Intracranial Hypertension and one of retrobulbar optic neuritis within one month during COVID-19 pandemic raises a possibility of COVID-19 triggered mechanism. Meta -analysis is needed to

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establish a causal relationship between COVID-19 and neuro-ophthalmic disease, and better understand pathogenesis.

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DECLARATIONS

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