Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 12, Page No: 026-030

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

The Aftermath of COVID-19: In Terms of Neuro Ophthalmic Manifestations

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ABSTRACT

The Coronavirus is also known as beta Coronavirus, COVID-19 as was first reported in Wuhan city, Hubei province of China in December 2019. However, named SARS-CoV-2 i.e., severe acute respiratory syndrome Coronavirus 2 as this virus resembles phylogenetically with SARS-CoV-2 emerging from the family of human Coronavirus, HCoV-2. It also shows similarity with MERS-CoV-2 (Middle East Respiratory Syndrome Coronavirus), a reason for a major worldwide outbreak in 2011.

COVID-19 caused a devastating pandemic declared as a global health emergency by WHO in March 2020 targeting the same old human respiratory system as SARS-CoV-2 and MERS with no cure in sight as it seemed. In recent years, it did an incredible amount of damage. Obvious enough warranting no mention. With the increasing involvement of various other systems, it has been linked to neuro ophthalmic complications. Due to emerging deaths and disability highlighted these complications which were then masked by other life threatening complications. Symptoms and signs of neuro ophthalmology can manifest alone or in conjunction with neurological diseases.

This article has aims to review various neuro ophthalmic manifestations seen in COVID-19 patients and the pathophysiology leading to these complications.

The following search terms were used to find relevant publications in the PubMed, Google Scholar and Journal of ophthalmology, eye and brain journal and other WHO databases using the relevant. A thorough manual search was made through articles and their references cited. Data and definitions from websites like NCBI and WHO were also taken in order to gain authentic information.

Key words: COVID-19, SARS-CoV-1, MERS, SARS-CoV-2, Ocular, Ophthalmology, Neuro ophthalmic manifestations, Neuro ophthalmology, Pathophysiology, Neurological, Manifestations

HOW TO CITE THIS ARTICLE: Punya Bharadwaj, Sonali Choudhari, The aftermath of COVID-19: In Terms of Neuro Ophthalmic Manifestations, J Res Med Dent Sci, 2022, 10 (12): 026-030.

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E-mail: punyab49@gmail.com
Received: 01-Sep-2022, Manuscript No. JRMDS-22-75749;
Editor assigned: 05-Sep-2022, PreQC No. JRMDS-22-75749 (PQ);
Reviewed: 19-Sep-2022, QC No. JRMDS-22-75749;
Revised: 21-Nov-2022, Manuscript No. JRMDS-22-75749 (R);
Published: 01-Dec-2022

INTRODUCTION

Coronaviruses, the name goes with a specific characteristic of having a crown shaped appearance seen microscopically. Coronavirus 2019 is a single stranded RNA virus part of the Coronavirinae subfamily, which includes four genera and seven Coronaviruses (CoV-2) species that have been reported to cause infections in people [1,2]. Among these most highly pathogenic Coronaviruses known to man are beta Coronaviruses, including SARS-CoV-2, MERS-CoV-2 and SARS-CoV-2. The alpha Coronaviruses are also associated with infections in humans while infections in birds are more typically linked with gamma Coronaviruses and delta Coronaviruses. Among these three SARS-CoV-2 and MERS-CoV-2 were noted to be transmitted through market civets (Colombia, Indonesia, Vietnam, Egypt, Turkey and South Africa) and Arabian camels, respectively, whereas SARS-CoV-2 was believed to be arising from the animal and seafood market in Wuhan, china also known as wet market. However, all three of them are, believed to be strongly linked with bats, despite the fact that confirming this has been challenging. If we were to talk about transmission among humans, it is also not much fixed to a specific mode of transmission, mostly by droplet infection, other mechanisms being fomites and airborne. Recent case reports have also connected Coronavirus disease-2019 (COVID-19) to ocular signs and symptoms so; there is a probability of ocular transmission, with the conjunctiva acting as both a route and a source of infection, according to research. During the on-going pandemic, an observational study in china involving 214 hospitalized patients concluded the relation of neurological manifestation in COVID-19 patients [3].

LITEARTURE REVIEW

Pathophysiology

Coronavirus is described as a virus with neuro trophic nature and a knack for neuro invasion. Hence, there is a reason to believe it could be blamed for neuro ophthalmic symptoms. However, the pathways by which it could reach the central nervous system are a controversial topic to be discussed. While some reports have suggested haematogenous dissemination of virus or a lymphatic route with the infected leukocytes serving as a vector and reservoir for its pathway to the central nervous system. There's another hypothesis that talks about a trans-neuronal retrograde infection propelling a nasal infection *via* ethmoid bone to the olfactory bulb [4].

The presence of angiotensin converting enzyme 2 receptors and their exploitation by the SARS-CoV-1 and SARS-CoV-2 is another such explanation that came out of multiple reports. These receptors are described as being present in aqueous humour which could be a potential target for the cascade of events.

Keeping all this in mind, the possibility of the role of a cytokine storm in question cannot be ruled out, causing a hyper inflammatory response throughout the body; a similar pattern could exist in the central nervous system leading to complications.

Moonis, et al. have also classified COVID-19 related central nervous system disorders into major categories as a result of direct infection. Which can occur by the processes like neuro invasion or endothelial dysfunction, coagulopathy and cytokine storm followed by the immune response at early exposure whereas, delayed immune activation after infection and complications are still yet to be explored well [5].

While the evidence is not as adequate as we would like it to be. It does pose a common ground that coronavirus can definitely be implicated in neuro inflammation, eventually leading to neuro ophthalmic manifestations and many more troublesome symptoms.

Clinical features

The symptoms of COVID-19 infection in humans show resemblance to those of other viral infections such as influenza and the common cold, making its diagnosis a bit more tedious task. The commonest and earliest symptoms are fever and cough [6]. Other reported clinical features are malaise, dry cough, sore throat, running nose, breathlessness, respiratory distress and generalized weakness, this could quickly develop into pneumonia. Various other extra pulmonary manifestations could also be seen for instance diarrhoea, arthralgia, myalgia, or headache. Some of the patients may even have an infection that seems to be asymptomatic [5].

Shifting the focus to the non-respiratory manifestations due to COVID-19. These are ocular, neurological and cerebrovascular diseases leading to visual disturbances, neuro ophthalmic, gastrointestinal, cardiovascular and acute kidney injury.

With recent and calculated studies various specific neurologic and neuro ophthalmic symptoms which came over the course of time are hypogeusia or ageusia, hyposmia or anosmia, headache, retro orbital pain, Ocular or periocular pain, diplopia (double vision, visual impairment, ocular cranial nerves palsy and ophthalmoplegia, nystagmus, optic neuritis pupillary defects other optic disc changes, cranial neuropathies, focal neurological deficits, Guillain-Barre, miller fisher syndrome and encephalopathy [5-8].

Various studies classify these complications from Afferent and efferent perspectives. Afferent optic neuritis, papilledema, papillophlebitis, Acute Demyelinating Encephalomyelitis (ADEM, brain infarct due to hypoxia, thromboembolism and cerebrovascular stroke causing loss of vision, haemorrhage, grey matter hypoxia, infectious meningitis or encephalitis, leukoencephalopathy, acute necrotizing haemorrhagic encephalopathy and Posterior Reversible Encephalopathy Syndrome (PRES resulting in visual impairment, pseudo tumour cerebral syndrome also called as Idiopathic Intracranial Hypertension (IIH. On imaging shows fundus nodule and various other changes on MRI [5,9].

Efferent complications encompass the following orbital abnormalities, nystagmus, cranial nerve palsies, neuropathies, diplopia, miller fisher syndrome, Guillain-Barre and other eye movement disorders occurring with rhomb encephalitis, Adie's pupils also called as Holmes Adie syndrome in which there is parasympathetic denervation and ocular myasthenia gravis (Table 1) [5,9].

Table 1: Complications according to afferent and efferent perspectives.

Afferent complications	Efferent complications
Optic neuritis,	cranial neuropathies
Papilledema	Orbital abnormalities
Pseudo tumour cerebral syndrome	Nystagmus
(ADEM) Acute Demyelinating Encephalomyelitis	Guillain-Barre Syndrome
Visual disturbance	Miller fisher syndrome
Encephalitis	ocular myasthenia gravis

Posterior Reversible Encephalopathy Syndrome (PRES).	Adie's pupils
Acute necrotizing haemorrhagic encephalopathy	

DISCUSSION

Optic neuritis: An inflammatory condition involving optic nerve causing demyelination presenting with loss of vision and unioccular pain, usually associated with multiple sclerosis. It is mostly unilateral and rarely bilateral [10].

It was demonstrated in rodents by Weve H, et al. in a research study on Lewis rats that Coronavirus infection in rodents can cause demyelination following the invasion of the central nervous system [11]. One such incidence reported and published by Mohammed A Azab, et al. in July 2021 presented a case of a 32-year-old male patient with chief complaints of a sudden loss of vision in his left eye, unilateral headache of throbbing nature, scotoma and raised intraocular pressure following COVID-19 positive status (RT-PCR positive) after two weeks.

On examination, visual acuity was found to be 20/200 on the left eye while that of the right eye was 20/30. Slit lamp showed no abnormalities in the anterior chamber and uvea. On fundus examination, there was mild disc oedema or papilledema while macula was normal.

OCT (Optical Coherence Tomography) showed mild swelling around the retinal nerve papilla, axial MRI revealed swelling of the left sided optic nerve.

Diagnosis of optic neuritis was made. Treatment given was 1 g methylprednisolone IV × 3 days, 60 mg tab prednisone for 1 week with tapering gradually. On follow up, there was good improvement seen but visual acuity and colour vision were not reverted back to the original vision of the patient [12]. Published in Nov 2020, Khalid swalha and Stephen adeodokun reported a case of bilateral optic neuritis of a 44 year old male. He presented with bilateral ocular pain which was progressive occurred first in one eye and later involved both and loss of vision after two weeks of testing positive for COVID-19.

Visual acuity of the right eye was 20/200 with RAPD (relative afferent pupil area defect) suggestive of global loss of vision. The left eye was 20/30 with superior accurate visual field defect. All routine laboratory tests were within normal limits. Axial orbital MRI revealed more enhancement and ill define optic nerve in the right eye than left suggestive of optic neuritis.

He was prescribed 1 gm methylprednisolone IV for 5 days OD. Later tapering of dose over 4 weeks. Improvement was remarkable within 48 hours. Follow up was advised [13].

In both, the cases patient was diagnosed with optic neuritis which was linked to COVID positive status and started on IV corticosteroids as soon as possible which made the recovery fast and remarkable. Follow up is necessary in order to scan for multiple sclerosis and other associated features which may present later. Another case of optic neuritis has also been reported which describes its association with ADEM [14].

Acute Disseminated Encephalomyelitis (ADEM): It is a monophasic autoimmune demyelinating disease involving the central nervous system, ethology being viral, bacterial infection, or a vaccination, predominantly affects children and young adults.

Through experiments on animals, it was concluded that inflammation of the CNS followed by demyelination occurs in response to not only primary but also secondary immune responses. It subsequently leads to the abrupt onset of multifocal neurological deficits.

This unspecific abrupt onset encephalopathy may be suspected if there is a change in behaviour or altered sensorium which may or may not be associated with fever. Neurological deficits are typically visual field deficits, hemiparesis and poly focal [14]. One such report by Langley L, et al. demonstrates a case of 53-year-old male who presented with complaints of cough, breathlessness, myalgia, fever and malaise since 8 days. With positive RTPCR, he went into respiratory failure within a day and had to be intubated. Over the course of the hospital stay he developed various complications like tension pneumothorax, DVTs and sepsis, AKI, he was sedated in view of severe agitation. On neurological examination, his eyes opening was spontaneous with b/l pupils reactive to light, right gaze preference with preservation of a normal doll's eye reflex. GCS score was low as no verbal response to pain was observed. He was hypotonic and exhibited no limb reflexes and decreased motor response. On MRI asymmetrical and bilateral hyper intense lesions within the deep white matter were seen which the hallmark of ADEM is. The diagnosis was made and was then started with Methylprednisolone 1 g IV for 3 days and subsequently 60 mg/day prednisolone and tapering it by 10 mg/week after which a maintenance dose of 20 mg was given. On follow up in 3 days, there was a significant improvement in GCS score. His hemiparesis also improved over 2 month's course [15]. The patient was advised for regular follow up as relapse may occur in spite of ADEM being a monophasic disease.

Visual disturbances or loss of vision: The same observational study in Wuhan described visual disturbances in 1.4% of the sample size [3]. Two cases were reported where visual impairment occurred after PRES in COVID positive patients who persisted even after rehabilitation. A case study by Alison M, et al. considered a 69-year-old female with comorbidities like HTN and dyslipidaemia who was RTPCR positive. She presented with cough and diarrhoea for 5 days. During the course, she went into respiratory failure and was intubated and

had seizure like episodes with leftward gaze deviation. Drugs prescribed were ceftriaxone for 7 days, azithromycin for 2 days, hydroxyl chloroquine for 4 days and hydrocortisone for 1 week with tapering by the end of the week. On MRI features suggestive of PRES were seen and a diagnosis was made. After extubation, visual symptoms like blurred vision, left side visual impairment, visual hallucinations and reading difficulties were noted. On examination, visual acuity was found to be normal while visual field loss was found as left homonymous hemianopia, which was still present even after duration of 12 months [16]. A similar case of a 55 year old female was presented. She complained of vertigo and acute vision loss followed by seizure and right gaze deviation. Radiologic findings were symmetrical hyper intense oedema in parietal and occipital lobes suggestive of PRES [16].

Posterior Reversible Encephalopathy Syndrome (PRES): PRES is a neurological syndrome, first described in 1996 which has a particular set of radiological findings. It clinically presents with headache, seizures, visual impairment, encephalopathy and focal neurologic deficits for e.g. hemiparesis, hemiplegia, difficulty in speaking, but not with a strict margin of symptoms. Pathophysiology being deranged auto regulation accompanied with endothelial dysfunction hence leads to hyper perfusion of the posterior circulation [17].

Cranial neuropathies, diplopia, ophthalmoplegia: COVID-19 has been reported to have ophthalmoplegia due to cranial nerve palsy and cerebrovascular event. A case of Inter nuclear Ophthalmoplegia (INO) was reported by Varshitha Hemanth Vasanthpuram, et al. who described a 58-year-old patient presenting with sudden onset diplopia in both eyes. And no other complaints in relation to COVID. On examination findings were: vertical diplopia, left beating nystagmus on abduction in the left eye, right eye adduction was limited which was suggestive of right sided INO. Other findings were normal except, for nasal pterygium in both eyes and a cataract in the left eye. On regular screening COVID test was found to be positive. Another differential like ocular myasthenia was ruled out clinically. The patient recovered without much intervention within 4 weeks [18]. Two cases by Marc Dinkin, et al. were reported with complaints of diplopia and ophthalmoplegia. In one case there was sixth cranial nerve palsy in both eyes, third cranial nerve palsy in the left eye, while another patient had sixth cranial nerve palsy in the right eye. Diagnosis of miller fisher syndrome was made [19].

Miller fisher syndrome: MFS is named after Charles miller fisher, a Canadian neurologist. It is defined by NCBI as a rare variant of Guillain-Barre Syndrome (GBS), a bigger term that includes immune mediated polyneuropathies. Its symptoms are ataxia, ophthalmoplegia and are flexia [20]. It is rare acquired nerve pathology with features including weakness of ocular muscles causing problems with eye movements; limb not being coordinated and unsteadiness; with an absence of tendon reflexes. Other symptoms might present as facial, swallowing and limb weakness, as well as respiratory failure. MFS can affect both children and adults. It often occurs several days (up to four weeks) after a bacterial or viral illness. MFS is rare, affecting one to two people per million each year. It is an autoimmune disease, in which the immune system attacks the nerves. Specific treatment is available but most patients recover within six months even without treatment. Very few patients have permanent neurological problems or relapses. Death is very rare.

Nystagmus: Nystagmus is defined as a condition where the eyes move rapidly in oscillatory movements which could be horizontal, vertical or rotatory. It could be slow or fast and typically manifests in both eyes. Multiple viruses have been previously implicated as a trigger of nystagmus namely cytomegalovirus and Zika virus in the paediatric population [21]. Patients usually turn or tilt their head to aid the vision. E Garcia Romo, et al. identifies a case of female in her 20s who happened to be in Italy when the emergency measures took place in the country, she returned to Spain and began experiencing upper respiratory tract symptoms that is fever, headache and anosmia soon after. After three weeks, she presented with dizziness spells and intermittently horizontal nystagmus with a rotatory component. All of her scans turned out to be normal and she was found to be COVID-19 positive which was being treated as sinusitis at initial presentation. Ophthalmological and otolaryngological examination remained uneventful except two episodes of nystagmus of about 10 s duration were observed in both eyes in a horizontal asymmetric pattern, more in the left eye which continued to increase in frequency.

CONCLUSION

The studies continue to revolve around the respiratory manifestation while neglecting the other symptoms which might not be as concerning if looked into and acted upon at an earlier stage. The case reports and the data draw a definite connection between Coronavirus and neuro ophthalmic symptoms. It can have a drastic impact on the central nervous system, hence the neurological and occurrence of neuro ophthalmic presentations should always be kept as a possibility in mind. We believe a large number of complications are hindered by the presence of life threatening scenarios in the picture for the affected individuals. To begin with, the clinicians should speculate ADEM in COVID-19 patients who develop any kind of neurological deficit and are slow to wake from the sedative stage. A thorough ophthalmic examination would provide a better prognosis. With patients developing a febrile illness, there may exist multiple differentials. However, cases of hemiparesis should raise suspicion for a crucial diagnosis of cerebral involvement, which could be cerebral abscess or encephalitis which is a prerequisite for MRI and lumbar puncture. An EEG could also be suitable, though non-specific. To conclude, even though the studies are limited and warrant more case reports and series, rather than isolated incidents. It provides us with a better outlook.

We should keep viral infections as a possible differential while dealing with such complications.

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