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Prevalence of Ophthalmic Manifestations in COVID-19 Positive Indoor Patients during Second Wave at Rural Tertiary Care Hospital of Gujarat: A Prospective Observational Study

Ophthalmology Section

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ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) can affect multiple system of body including eye. In eye, it can cause mild conjunctivitis, posterior segment involvement, neuro-sensory involvement and lethal opportunistic infection like mucormycosis. Associated co-morbidities, severity of COVID-19 infection and corticosteroids used in its management can affect ophthalmic involvement.

Aim: To determine the frequency and various types of ophthalmic manifestation of patients with COVID-19.

Materials and Methods: This prospective observational study was conducted on indoor patients of Shree Krishna Hospital, a rural, tertiary care hospital affiliated with Pramukh Swami Medical College, Karamsad, Gujarat, India, from 1st May 2021 to 1st January 2022. Second wave of COVID-19 was from 13th March 2021 to 19th June 2021. Patients' demographic data, details of COVID-19 infection severity score, oxygen requirement, use of corticosteroids, history of various co-morbidities and stages of Rhino-Orbital-Cerebral Mucormycosis (ROCM) (if present) were noted. Bedside ophthalmic examination was done with torch light, fluorescent strip, cobalt blue light of direct ophthalmoscope and fundus examination with indirect ophthalmoscopy under institutional COVID-19 guidelines. Descriptive Statistics {Mean, (SD), Frequency, (%)} were used for analysis of the collected data.

Results: Out of 649 COVID-19 patients, 368 were male and 281 were female with mean age of 52.58 (±15.38) years. All over prevalence of ophthalmic manifestations was 9.86% (n=64 out of 649 patients). A total of 63 patients (9.71%) did not require any oxygen supplement, 352 patients (54.24%) required nasal prongs, 201 patients (30.97%) required non invasive ventilator support and 33 patients (5.08%) required mechanical ventilation. The 378 patients (58.24%) received corticosteroids in oral or intravenous form. A total of 325 patients (50.1%) had diabetes, 267 patients (41.1%) had hypertension, 29 patients (4.5%) had chronic kidney disease and 15 patients (2.3%) had thyroid disease. A total of 52 patients (8.01%) had conjunctivitis. Mean age of patients with conjunctivitis was 50.04 (±15.28) with male preponderance (n=30, 57.7%). Most common systemic presentation was fever (n=29, 55.8%). Patients with conjunctivitis had high D-dimer (>500 ng/mL) (n=42; 80.8%) and C-Reactive Protein (CRP) values (>3 mg/L) (n=39; 75%). A total of 144 patients (22.2%) were vaccinated with COVID-19 vaccine first dose while 10 patients (19.23%) out of 52 patients having conjunctivitis were vaccinated. Out of 649 patients, prevalence of ROCM was 1.85% (n=12) with mean age 58.58 years (±9.71 years) and male preponderance (n=8, 66.66%). Nine out of 12 patients had high blood sugar levels (mean level 340 mg/dL) at the time of admission. Out of 12, eight patients had received corticosteroids for management of COVID-19 infection. Six patients of ROCM (50%) did not require any oxygen support while two patient (16.7%) required nasal prongs for mean 7.50 days and four patient (33.3%) required non invasive ventilator support for mean 7.33 days (±2.5 days). One patient had stage 2C disease, one had stage 3B, five patients had stage 3C while five patients had stage 4C disease.

Conclusion: Ocular manifestations of COVID-19 range from conjunctivitis to ROCM. Conjunctivitis has mild and self-limited course while ROCM is sight threatening and life-threatening condition, if not treated appropriately.

Keywords: Coronavirus disease-2019, Conjunctivitis, Corticosteroids, Rhino-orbital-cerebral-mucormycosis

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in a few unusual pneumonia patients linked to the Wuhan seafood wholesale market in China in December 2019 [1]. However, it soon grew out of China and the Coronavirus Disease 2019 (COVID-19) was declared a pandemic on 11th March 2020, and has been reported in 216 countries, areas or territories including India.

Symptoms of COVID-19 can range from fever, cough, loss of taste and smell, sore throat, headache, diarrhoea, skin rashes to more severe symptoms like chest pain and breathlessness [1]. Apart from other systems, COVID-19 can affect patient's eye in many ways [2]. COVID-19 associated conjunctivitis can occur due to direct contact with a person having COVID [3,4]. Symptoms range from watering, foreign body sensation, red eye or can be asymptomatic. Signs of COVID-19 conjunctivitis includes congestion and follicular reaction. Disease usually resolves without any complication but epithelial keratitis, pseudo membrane or haemorrhagic conjunctivitis can occur. Tender lymphadenopathy can also occur [5].

Central retinal artery and vein occlusion are posterior segment findings which are associated with COVID-19 disease. Other retinal findings seen in COVID-19 are cotton wool spots and haemorrhages [6]. Afferent visual pathway defect includes papillo-phlebitis, optic neuritis, papillo-oedema and posterior reversible encephalopathy [7]. Miller-Fischer syndrome, cranial neuropathies, Adie's pupil, ocular myasthenia gravis and nystagmus are possible efferent neuro-ophthalmic complications [8].

Mucormycosis is an opportunistic, potentially lethal angio-invasive fungal infection. They are of pulmonary, cutaneous, gastro-intestinal, disseminated or rhino-orbital cerebral type. Out of which

rhino-orbital-cerebral type is most common [9]. Prolonged use of corticosteroids, poorly controlled diabetes mellitus, lung diseases, malignancy and the immunocompromised state aggravates secondary infections [9,10]. Spores are inhaled through nasal cavity and spread to para-nasal sinuses via breach in mucosa. Through para-nasal sinuses they invade orbit through lamina paparycea, inferior orbital fissure, infratemporal fossa or orbital apex. Intracranial invasion occurs through superior orbital fissure, cribriform plate of ethmoid bone or perineural invasion [11]. Hence, the present study was conducted with an aim to determine the frequency and various types of ophthalmic manifestation of patients with COVID-19.

MATERIALS AND METHODS

This prospective observational study was conducted on indoor patients of Shree Krishna Hospital, a rural, tertiary care hospital affiliated with Pramukh Swami Medical College, Karamsad, Gujarat, India, from 1st May 2021 to 1st January 2022. Second wave of COVID-19 was from 13th March 2021 to 19th June 2021. A total of 649 patients with COVID-19 were included in this study with no exclusion. Two out of 649 patients had unilateral proptosis, an ophthalmic manifestation and none had conjunctivitis at the time of admission as per medical records. After getting approval and clearance from the Institutional Ethics Committee (IEC/BU/130/FACULTY 15/171), the participants were enrolled in the study with their verbal consent.

Study Procedure

Patients' demographic data (age and sex), details of COVID-19 infection severity score was determined on the basis of Computed Tomography (CT) severity score, oxygen requirement, use of corticosteroids, history of various co-morbidities and stages of ROCM (if present) were noted. Bedside gross anterior segment examination was done with torch light. Ocular surface examination was done with fluorescent strip, cobalt blue light of direct ophthalmoscope and fundus examination with indirect ophthalmoscopy under institutional COVID-19 guidelines.

COVID-19 infection severity was categorised as follows [12] on bases of CT severity score:

mild: <7

moderate: 7-18

severe: >18

Neutrophil to Lymphocyte ratio (N/L ratio) was categorised as follows [13]:

<6: normal

6-9: mild elevation

9-18: moderate elevation

>18: severe elevation

In this study staging of ROCM was based on classification proposed by OPAI-IJO study [Table/Fig-1] [11].

Proven ROCM was defined as clinico-radiological features along with microbiological confirmation on direct microscopy and/or culture or histopathology with special stains or molecular diagnostics.

Alive with disease regression terminology is used when severity and spread of disease decreases after treatment. Alive with disease progression is used when severity and spread of disease increases after treatment. Stable residual disease terminology is used when after treatment disease remains same with no increase or decrease. (As per the terminology used in OPAI-IJO study) [11].

STATISTICAL ANALYSIS

As nature of the study was exploratory, descriptive statistics {Mean (SD), Frequency (n) and percentages (%)} were used to portray the profile, management and outcome of study population. Statistical Software (STATA (14.2)) was used for this study.

RESULTS

All over prevalence of ophthalmic manifestations was 9.86% (n=64 out of 649 patients) [Table/Fig-2].

Staging of Rhino-Orbital-Cerebral Mucormycosis (ROCM)
Stage 1: involvement of the nasal mucosa 1a: limited to the middle turbinate 1b: involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: involvement of the nasal septum 1d: bilateral nasal mucosal involvement
Stage 2: involvement of paranasal sinuses 2a: one sinus 2b: two ipsilateral sinuses 2c: > two ipsilateral sinuses and/or palate/oral cavity 2d: bilateral paranasal sinus involvement or involvement of the zygoma or mandible
Stage 3: involvement of the orbit: 3a: nasolacrimal duct, medial orbit, vision unaffected 3b: diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: central retinal artery or ophthalmic artery occlusion, superior ophthalmic vein thrombosis; involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: bilateral orbital involvement
Stage 4: involvement of the CNS: 4a: focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: multifocal or diffuse CNS disease

[Table/Fig-1]: Staging of Rhino-Orbital-Cerebral Mucormycosis (ROCM).
CNS: Central nervous system

Ophthalmic manifestations	Prevalence
Overall	9.86% (n=64)
Conjunctivitis	8.01% (n=52)
ROCM	1.85% (n=12)

[Table/Fig-2]: Prevalence of ophthalmic manifestations.

Amongst total patients, 144 patients (22.2%) were vaccinated with COVID-19 vaccine first dose while ten patients (19.23%) out of 52 patients having conjunctivitis were vaccinated with first dose of COVID-19 vaccine.

A total of 368 (56.70%) were male and 281 (43.30%) were female with mean age of 52.58 (±15.38) years [Table/Fig-3]. Total 131 patients (20.18%) had mild COVID-19 infection severity score, 301 patients (46.38%) had moderate, and 217 patients (33.44%) had severe COVID-19 infection severity score. The 63 patients (9.71%) did not require any oxygen supplement, 352 patients (54.24%) required nasal prongs, 201 patients (30.97%) required non invasive ventilator support and 33 patients (5.08%) required mechanical ventilation. A total of 378 patients (58.24%) received corticosteroids in oral or intravenous form while 271 patients (41.76%) had not received corticosteroids. The 325 patients (50.1%) had diabetes, 267 patients (41.1%) had hypertension, 29 patients (4.5%) had chronic kidney disease and 15 patients (2.3%) had thyroid disease [Table/Fig-4].

Age (years)	Male patients n (%)	Female patients n (%)
Total 649 patients		
52.58 (±15.38)	368 (56.70%)	281 (43.30%)
52 patients with conjunctivitis		
50.04 (±15.28)	30 (57.70%)	22 (42.30%)
12 patients with ROCM		
58.58 (±9.718)	8 (66.66%)	4 (33.34%)

[Table/Fig-3]: Age and sex distribution of subjects.

Patients having conjunctivitis presented with systemic symptoms like fever (n=29, 55.8%), headache (n=22, 42.3%), cough (n=29, 55.8%), cold (n=29, 55.8%), fatigue (n=19, 36.5%) and breathlessness (n=22, 42.3%) [Table/Fig-5].

Co-morbidities	Diabetes	Hypertension	Chronic kidney disease	Thyroid disease
Total patients (N=649)	325 (50.1%)	267 (41.1%)	29 (4.5%)	15 (2.3%)
Patients with conjunctivitis (n=52)	25 (48.1%)	19 (36.5%)	4 (7.7%)	0
Patients with ROCM (n=12)	7 (58.33%)	4 (33.33%)	1 (8.33%)	0

[Table/Fig-4]: Frequency distribution of associated co-morbidities.
ROCM: Rhino-orbital-cerebral mucormycosis

Variables	Patients with conjunctivitis n (%) (n=52 patients)	Patients with ROCM (n=12 patients)
Systemic symptoms		
Fever	29 (55.8%)	9
Cough	29 (55.8%)	10
Cold	29 (55.8%)	10
Headache	22 (42.3%)	2
Fatigue	19 (36.5%)	4
Breathlessness	22 (42.3%)	5
Ocular symptoms		
Watering	10 (19.2%)	9
Pain and foreign body sensation	9 (17.3%)	6
Itching	7 (13.5%)	3
Blurring of vision	5 (9.6%)	10
No symptoms	21 (40.38%)	0
Biochemical parameters		
D-dimer level >500 ng/mL	42 (80.8%)	11
CRP level >3 mg/mL	39 (75%)	12
N/L ratio		
Severe elevation	3 (5.8%)	12
Moderate elevation	28 (53.8%)	
Mild elevation	15 (28.8%)	

[Table/Fig-5]: Frequency distribution of systemic symptoms, ocular symptoms and biochemical parameters in patients with conjunctivitis and ROCM.

Most common ocular symptoms among patients with conjunctivitis was watering (n=10, 19.2%) followed by pain and foreign body sensation (n=9, 17.3%), itching (n=7, 13.5%) and blurring of vision (n=5, 9.6%). In rest of the patients, no symptoms were present [Table/Fig-5]. Out of 52 patients having conjunctivitis, 42 patients (80.8%) with had D-dimer levels >500 ng/mL at the time of admission, while 39 patients (75%) had increased CRP levels (>3 mg/L) [Table/Fig-5].

Out of 52 patients of conjunctivitis, 3 patients (5.8%) had severe elevation (>18) in N/L ratio, 28 patients (53.8%) had moderate elevation (9-18), 15 patients (28.8%) had mild elevation (6-9) in N/L ratio. Rest six patients had normal N/L ratio. A total of 25 patients (48.1%) were known case of diabetes at the time of admission. A total of 15 patients (28.8%) had HbA1c value of >6.4% at the time of admission and 10 patients (19.2%) had value of pre-diabetic range (5.7%-6.4%). Other co-morbidities were hypertension (n=19, 36.5%) and chronic kidney disease (n=4, 7.7%).

ROCM Data

Out of 12 patients of mucormycosis, eight patients were male (66.7%) with mean age of 58.58 years (±9.71) [Table/Fig-3]. Mean number of days from COVID-19 diagnosis to starting of ROCM symptoms are 12 (±2.6) (median: 10). Seven out of 12 patients had diabetes, 4 had hypertension and 1 had chronic kidney disease [Table/Fig-4].

Out of twelve patients of ROCM, 10 patients had cough and cold, nine patients had fever, five patients had breathlessness, four patients had fatigue and two patients had headache [Table/Fig-5]. Blurring of vision was most common ocular symptom (n=10) followed by watering (n=9), pain and foreign body sensation (n=6) and itching (n=3) [Table/Fig-5]. Out of 12 patients of ROCM, 11 patients had D-dimer levels >500 ng/mL at the time of admission while all 12 of them had increased CRP levels (>3 mg/L) and severe elevation (>18) of N/L ratio [Table/Fig-5].

Out of 12 patients, nine patients (75%) presented with orbital oedema followed by ptosis (n=7, 58.3%), orbital pain (n=2, 16.7%) and loss of vision (n=2, 16.7%). One patient had proptosis. Partial ophthalmoplegia involving III and VI nerve was seen in one patient (8.3%) and total ophthalmoplegia involving III, IV and VI nerve was seen in 9 patients (75%). One patient had trigeminal neve involvement and one patient had facial nerve involvement. Mean no. of days to develop ROCM symptoms from COVID-19 diagnosis were 12 (median: 10). One patient had stage 2C disease, one had stage 3B, five patients had stage 3C while five patients had stage 4C disease.

In present study, seven (58.3%) out of twelve patients of ROCM had pre-existing diabetes mellitus. On admission nine patients (75%) had high blood sugar level (mean HbA1c value 8.7%) out of which three were controlled by insulin and six patients had uncontrolled sugars with insulin. Mean HBA1c level of all 12 patients of ROCM was 10.75%.

Six patients of ROCM (50%) did not require any oxygen support while two patient (16.7%) required nasal prongs for mean 7.50 days (±3.54 days) and four patients (33.3%) required non invasive ventilator support for mean 7.33 days (±2.5 days). Maxillary sinus was most commonly involved sinus (n=6, 50%) as detected by Magnetic Resonance Imaging (MRI) scan followed by ethmoid sinus (n=4, 33.3%). One patient (8.3%) had pan sinus involvement. One patient (8.3%) had bilateral ethmoid, left-sided maxillary and left half of sphenoid sinus involvement.

Inferior orbital wall was most commonly involved (n=4, 33.3%) followed by medial orbital wall (n=3, 25%). Involvement of all four orbital walls was seen in one patient (8.3%). Temporal lobe involvement in MRI was seen in five patients (41.7%). One patient had skull base involvement (8.3%). One patient (8.3%) had pan sinusitis (stage 2C), one patient (8.3%) had diffuse orbital involvement (stage 3B), five patients (41.7%) had inferior orbital fissure and orbital apex involvement along with loss of vision in (stage 3C), and five patients (41.7%) had intracranial extension in the form of internal carotid artery invasion and skull base involvement (stage 4C). All patients had unilateral ocular involvement, in which right eye involvement was seen in five patients (41.66%) and left eye involvement in seven patients (58.34%). Four patients (33.3%) had no light perception in affected eye, two patients (16.7%) had only light perception and six patients (50%) had vision between (20/40 to 20/100). Optic nerve compression as confirmed by MRI study was the main cause of visual dysfunction in four patients with no light perception and two patients with light perception only.

In present study, one patient (8.3%) with diffuse orbital involvement was treated with FESS as primary management and showed disease regression. Three patients (25%) required FESS with exenteration, out of which two had Central Nervous System (CNS) involvement and one patient had orbital involvement. One patient with CNS involvement had stable disease while one was dead. Patient with orbital involvement who underwent FESS with exenteration had stable disease. Patient with CNS involvement who did not have any surgical intervention showed disease progression (n=2). No patient was given sinus irrigation or retrobulbar Amphotericin B. One patient was given step down therapy. Mean duration of hospital stay for ROCM treatment was 18.64 days (Median: 13 days).

After the due course of treatment one patient was alive with regression, five patients were alive with stable residual disease,

two patients were alive with disease progression and four patients died. The authors had four patients in whom vision was salvaged (with final visual acuity between 20/40 to 20/100). Out of which two patients was given Amphotericin B as primary management, one patient was given FESS as primary management and one patient was given oral Posaconazole as primary treatment.

DISCUSSION

In present study, out of 649 COVID-19 patients, the analysed overall prevalence of ophthalmic manifestations was 9.86% (n=64 out of 649 patients). Out of 649 patients, 52 patients (8.01%) had conjunctivitis and 12 patients (1.85%) had ROCM. In a study done by Sindhuja K et al., prevalence of conjunctivitis was 6.29% (8 out of 127 patients) [14]. In a study done by Wu P et al., kumar KK et al., prevalence of conjunctivitis was 31.6% (12 out of 38 patients) and 0.72% (20 out of 2742) respectively [15,16]. In present study mean age of patients with conjunctivitis was 50.04 with male preponderance (n=30, 57.7%) while in a study done by Wu P et al., out of 12 patients of conjunctivitis, seven were males with median age of 67 (52 to 76) years [15].

In the present study, the most common systemic symptom in patients with conjunctivitis was fever (n=29, 55.8%). In a study done by Sindhuja K et al., cough (n=40, 31.49%) was the most common systemic symptom followed by the sore throat (n=10, 7.87%) and fever (n=6, 4.72%) in patients with conjunctivitis [14].

The most common ocular symptom was watering (n=10, 19.2%) followed by pain and foreign body sensation (n=9, 17.3%), itching (n=7, 13.5%) and blurring of vision (n=5, 9.6%). In a study done by Sindhuja K et al., out of eight patients of conjunctivitis, three patients (37.5%) had complaint of watering and out of these three patients one patient (12.5%) had complaint of itching [14].

In a study done in Germany by BostanciCeran B and Ozates S, 20 out of 93 patients (21.50%) having ocular involvement had significantly higher levels of N/L ratio (7.5±11.5) [17]. In present study, out of 52 patients having conjunctivitis, 46 patients (88.46%) had higher levels of N/L ratio (>6) [Table/Fig-5].

In present study, seven (58.3%) out of 12 patients of ROCM had pre-existing diabetes mellitus. On admission nine patients (75%) had high blood sugar level (mean level 340 mg/dL) out of which three were controlled by insulin and six patients had uncontrolled sugars with insulin. Mean HBA1c level was 10.75%. Hyperglycaemia was aggravated in uncontrolled diabetics. Corticosteroids used in treatment of COVID-19 causes further hyperglycaemia and immunosuppression [18]. Hyperglycaemia causes glycosylation of transferrin and ferritin and thus free iron level increases. All this led to acidic environment, which is favourable for fungal growth. Diabetes is independent risk factor for ROCM. In a prospective observational case series done by Sharma S et al., out of 23 patients of ROCM, 21 patients had diabetes and 12 were having uncontrolled blood sugars [19]. In a study done by Patel A et al., the most common associated co-morbidity was diabetes mellitus among both ROCM and non ROCM groups (62.7%) [20].

In OPAI-IJO all India collaborative case study, the mean interval for onset of symptoms of ROCM from diagnosis of COVID-19 was found to be 14.5±10 days. ROCM can occur in post COVID-19 state (3 months after diagnosis of COVID). The mean age was 51.9 years (range: 12-88 years) with male preponderance (n=1993 out of 2826 patients) [11]. In present study, mean number of days to develop ROCM symptoms from COVID-19 diagnosis were 12 (median: 10), the mean age was 58.58 years with male preponderance (n=8, 66.7%).

In present study, out of 12 patients of ROCM, most commonly observed ocular symptoms were orbital oedema followed by orbital pain and loss of vision. Most common ocular signs were orbital oedema followed by ptosis, facial discoloration and loss of vision. Out of twelve patients, one patient had partial ophthalmoplegia and nine patients had total ophthalmoplegia. Out of nine patients of total ophthalmoplegia, one patient had associated trigeminal nerve involvement and one patient had associated facial nerve involvement. In a study done by Roushdy T and Hamid E at Egypt, out of 4 patients of ROCM, all patients had ptosis,3 had total ophthalmoplegia and 2 had decreased visual acuity [21]. Fouad YA et al., had studied 12 case of ROCM in which most common presenting signs were orbital-oedema and conjunctival chemosis (50%) followed by diminution of vision (41.7%), facial oedema (25%), nasal crusts (25%), total ophthalmoplegia (16.7%) and paralytic esotropia (8.3%) [18].

In present study, eight patients (66.6%) of ROCM had received corticosteroids, out of which one patient (8.3%) was given oral steroids for 21 days and seven (58.3%) patients were given intravenous steroids for mean 6.43 days. Intravenous methyl prednisolone was given to six (50%) patients and intravenous dexamethasone to one (8.3%) patient. Seven (58.3%) patients were given Remdesivir for 5.86 mean days. In a study done by Singh Y et al., eleven out of thirteen patients had received intravenous corticosteroids [22].

In present study, out of twelve patients, eleven patients (91.7%) were given liposomal Amphotericin B as primary treatment for mean 7.8 days (±5 days). Dose of Amphotericin B was calculated on the basis of weight of patient and state of renal involvement. One patient (8.3%) was given oral Posaconazole treatment for 5 days.

Limitation(s)

Due to single center study, the incidence of ocular manifestation may differ from multicenter study.

CONCLUSION(S)

The COVID-19 infection can affect eye in various ways, from common eye disease like conjunctivitis to severe life threatening and sight threatening disease like ROCM. Though incidence of ROCM is less as compared to conjunctivitis, it has lethal mortality rate.

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