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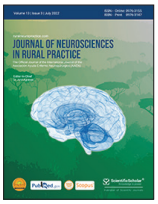

Original Article

Clinicoradiological profile and outcome of cavernous sinus syndrome with coronavirus disease-2019-associated rhino-orbito-cerebral mucormycosis

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ABSTRACT

Objective: With coronavirus disease 2019 (COVID-19) pandemic across the world, there had been an exponential increase in rhino-orbito-cerebral mucormycosis (ROCM). Extension of infection to cavernous sinus leads to cavernous sinus syndrome (CSS). This study aims to describe incidence, clinicoradiological profile, and outcome of CSS positive along with comparative analysis of CSS negative COVID-19-associated ROCM.

Material and Method: This was a prospective and observational study conducted from May 1, 2021, to July 31, 2021. Subjects included ROCM with active or recovered COVID-19 (past 6 weeks) and were categorized and staged. CSS was defined as involvement of two or more of third, fourth, fifth, or sixth cranial nerve with one each direct and indirect qualitative neuroradiological features. Clinicoradiological features of CSS-positive and negative COVID-19-associated ROCM groups were compared.

Results: Incidence of CSS with COVID-19-associated ROCM was 28%. Mean age of subjects was 44 ± 15 years with 60% being males and 73% were proven ROCM. Significant differences seen across the CSS-positive and negative groups were ocular, nasal, and cerebral findings including eyelid and periocular discoloration, ptosis, proptosis, ophthalmoplegia, nasal discharge, mucosal inflammation, and fever. Oculomotor, trochlear, and abducens nerves were significantly involved more in CSS-positive group. Significant radiological findings across two groups included indirect features in orbit, nose, and paranasal sinuses along with direct features in cavernous sinus. Surgical intervention was more common in CSS-positive group. Mortality in CSS-positive group at 8–24 weeks was 13 and 27%, respectively.

Conclusion: Extension of ROCM to CSS was more common in young males in advanced stages of proven ROCM with concurrent COVID-19. CSS-positive group had significant difference in clinicoradiological features involving orbit, nose, paranasal sinuses, and central nervous system as compared to CSS-negative group. This study highlights the need to develop an objective scoring system considering clinical and radiological features for diagnosis of CSS with COVID-19-associated ROCM.

Keywords: Cavernous sinus syndrome, COVID-19-associated ROCM, COVID-19, Rhino-orbito-cerebral Mucormycosis, Cavernous sinus, Neuroinfections

INTRODUCTION

During the pandemic of coronavirus disease 2019 (COVID-19) across the world since 2019, there is an exponential increase in the opportunist fungal infection-rhino-orbito-cerebral mucormycosis (ROCM).[1-3] This is an acute angioinvasive infection caused by fungal order Mucorales in patients with a background of immunocompromised conditions such as uncontrolled diabetes mellitus, use of corticosteroids and immunosuppressive drugs, immunodeficiency states, hematological malignancies, solid organ malignancies, or transplantation.[1] Concurrent COVID-19 provides a metabolically suitable environment for the growth of inhaled sporangiophores to germinate into hyphae and spread through tissue invasion, thrombosis, and necrosis to adjoining areas.[4]

The spectrum of ROCM ranges from limited nasal and paranasal sinuses or rhino-orbital disease to widespread rhino-orbito-cerebral disease central Nervous system (CNS involvement).[5,6] In India, the prevalence of mucormycosis (0.14 cases/1000 population) has been more than the developed nations and contributed to 80% of COVID-19-associated ROCM during second peak of pandemic.[1] The extension of infection to brain increases mortality rate of ROCM to 60%, but with early and aggressive surgical and medical treatment, it can be reduced to 30%.[7,8] CNS involvement occurs in 21–37% of ROCM by various routes of spread of infection

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including sinuses, blood vessels, nerves, cribriform plate of ethmoid bone, or pterygopalatine fossa.[9,10]

Involvement of cavernous sinus by ROCM leads to cavernous sinus syndrome (CSS). CSS is a group of signs and symptoms involving variable combinations of cranial nerves 3, 4, 5, and 6 along with oculosympathetic and parasympathetic plexii in cavernous sinus.[11] Cavernous sinus is a dangerous and difficult site for treatment and surgery due to its complex neurovascular structures. There are various causes of CSS including vascular diseases, neoplasms, infections, and inflammatory diseases. In Indian scenario, infections especially fungal constitutes an important etiology for CSS.[12] There is insufficient data on clinicoradiological description of involvement of cavernous sinus in COVID-19-associated ROCM. To the best of our knowledge, there had not been any prospective study on CSS in ROCM and present day scenario urges for one to understand the clinical progression of the disease.

This study aims to describe incidence and clinicoradiological profile and outcome of CSS-positive along with comparative analysis of CSS-negative COVID-19-associated ROCM. The early recognition of clinicoradiological features suggestive of CSS in COVID-19-associated ROCM may affect the course of an otherwise potentially fatal disease.

MATERIALS AND METHODS

This prospective and observational study was conducted in the division of neurology in a tertiary level hospital from resource limited rural belt of North India. This 600 bedded hospital is a dedicated Level III center for the management of COVID-19.

The study was conducted from May 1, 2021, to July 31, 2021, during the second peak of COVID-19 pandemic. The study sampled consecutive active (positive SARS-CoV-2 on reverse-transcription polymerase chain reaction analysis in the nasopharyngeal or oropharyngeal swabs) or recovered COVID-19 in the past 6 weeks with features suggestive of ROCM [Supplementary file-Annexure 1]. The study excluded subjects who were more than 6-week post-COVID-19 infection and had any other cause of CSS such as neoplasm, inflammation, or bacterial infections to avoid the selection bias.

ROCM was diagnosed and categorized as: [13]

- Possible cases: Clinical features suggestive of ROCM with background of concurrent or recently (<6 weeks) diagnosed case of COVID-19.
- Probable cases: Features in possible category and positive findings on diagnostic nasal endoscopy or neuroimaging.
- Proven cases: Features in probable category and microbiological confirmation of mucormycosis on direct microscopy, culture growth, or histopathological examination with special stains.

Staging of ROCM was done as proposed in a recent editorial by Honavar *et al*.[13]

ROCM was divided into CSS-positive and negative group depending on the involvement of cavernous sinus. CSS was defined as group of signs and symptoms suggestive of involvement of two or more of third, fourth, fifth (V1 and V2), or sixth cranial nerve with each one direct and indirect qualitative neuroradiological features [Supplementary file-Annexure 2]. The proposed neuroradiological features were prepared after a thorough literature review.[14-16] CSS was classified using Ishikawa classification [Supplementary file-Annexure 3].[12,14]

Clinical examination, procedures, and investigations were done using recommended government guidelines for COVID-19. Verbal and written informed consent was taken from subjects or her/his guardians. Clinicodemographic profile included age, gender, residential address, occupation, and presenting complaints. Ophthalmological, neurological (including higher mental functions, cranial nerves, motor, sensory, and extrapyramidal system), and ear, nose, and throat examination was performed. Vision loss was defined as visual acuity lower than finger counting at less than a half meter. The laboratory investigations included blood cell counts, hepatic and renal function tests, fasting lipid profile, and chest x-ray. Diagnostic nasal endoscopy was done for tissue diagnosis.

Neuroimaging included either computerized tomography (CT scan) head and orbit (Siemens Somatom Perspective 128 slice) or magnetic resonance imaging of brain (MRI brain) (Siemens Magnetom Avanto 1.5 Tesla). Magnetic resonance venogram was done in patient with high index of suspicion of venous thrombosis and clinically stable to be shifted to the radiology department. The contrast-enhanced neuroimaging was done only in subjects with normal renal function tests. The imaging studies were assessed for features suggestive of ROCM and CSS independently by a trained radiologist with an experience of 8 years, and a final diagnosis was reached after discussion and consensus with multidisciplinary team consisting of neurologist, ophthalmologist, otorhinolaryngologist, and neurosurgeon.

The short-term outcome was assessed at 8 weeks as good, if discharged from the hospital with clinicoradiological improvement and no further progression of disease. Poor outcome included expired, referred, or left against medical advice for any reasons. The long-term outcome for mortality was assessed with a telephonic follow-up at 24 weeks.

This study aims to describe incidence and clinicoradiological profile and outcome of CSS along with comparative analysis of CSS-negative COVID-19 associated ROCM. The null hypothesis assumed no difference for sociodemographic and clinicoradiological profile variables across these patient groups.

The patient data pertaining to sociodemographic and other clinical variables were entered in the form of a data matrix in

Microsoft® Excel® and analyzed using IBM® SPSS® v 20.0.0. The descriptive statistics were presented as frequencies and percentages/means and standard deviations as appropriate. Chi-square/Fisher's exact test was used to assess association among categorical variables and Independent Samples T test/ Mann–Whitney U test for exploring difference of continuous variables across two groups. A two-sided $P < 0.05$ was considered as statistically significant.

RESULTS

There were a total 2190 of COVID-19-associated admissions during the study period.

After screening, 54 subjects with COVID-19-associated ROCM were selected [Figure 1]. Incidence of CSS in COVID-19-associated ROCM was 28% (bilateral CSS in 27%) with whole cavernous sinus being most common site. Incidence of ROCM in COVID-19 was 2.4%.

[Table 1] shows clinicoepidemiological and risk factors profile of CSS-positive and negative groups. A statistically significant number of CSS positive group were in advanced stages of ROCM as compared to CSS-negative group ($P < 0.005$). Mean age in CSS-positive group (44 ± 15 years) was significantly lower than CSS-negative subjects (52 ± 11 years). Duration of symptoms onset (Median=10 days) was significantly longer in CSS-positive group. Only 1 subject (2%) had received first dose of COVID-19 vaccination and none had received two doses.

Clinical features of ocular and nasal findings including eyelid, periocular, and facial discoloration (n = 15.100%), ptosis (n = 12.80%), ophthalmoplegia (n = 12.80%), proptosis (n = 9.60%), and nasal discharge and mucosal inflammation (n = 5.33%) were significantly more common in CSS-positive as compared to CSS-negative group. Oculomotor (n = 13.87%), trochlear (n = 10.67%), and abducens nerve (n = 12.80%) were involved significantly more in CSS-positive group [Table 2]. Dilated fundus examination could be done in only ten subjects (18%) due to severe chemosis, proptosis, and hazy status of cornea in majority of these subjects. Fundus examination was normal in 70% and optic atrophy was seen in one subject each in CSS-positive and negative group.

MRI brain, MRI brain with gadolinium contrast, and both CT and MRI brain were performed more commonly in CSS-positive group. Significant indirect qualitative radiological findings in the orbit were fat and muscle infiltration, enhanced soft-tissue mass in orbital apex, proptosis, pre-septal cellulitis, enhancement of orbital muscles, and optic neuritis [Table 3].

Sphenoid and frontal sinus opacification and mucosal thickening, soft-tissue infiltration of maxillary periantral fat planes, involvement of infratemporal fossa, air fluid level in sinuses, and bony dehiscence of sinuses were significant findings in CSS-positive group. The direct qualitative features in CSS-positive group were abnormal signal intensity, convexity of lateral wall, filling defects, and internal carotid artery stenosis in 13 (87%), 12 (80%), 9 (60%), and 7 (47%), respectively. MR venogram could be done in 20% (n = 3) subjects which showed abnormal signal intensity in cavernous sinus and prominent superior ophthalmic vein [Table 3].

Management including surgical intervention with maxillectomy (n = 2 [13%]), orbital exenteration (n = 4 [27%]), and evisceration of eye (n = 3 [20%]) and use of intravenous liposomal or deoxycholate amphotericin-B and were performed significantly more in CSS-positive group. Clinical stability or regression of disease was seen in 53% (n = 8) and were discharged from the hospital. In CSS-positive group, mortality rate at 8 and 24 weeks was 13 and 27%, respectively [Table 1].

DISCUSSION

This study showed CSS in 28% (n = 15) of COVID-19-associated ROCM similar to the previous reports.[17,18] COVID-19 pandemic witnessed an exponential increase in coexisting infection with ROCM and extension to brain significantly affected the outcome.[9,10,19] This study showed significant differences in clinical features of CSS-positive as compared

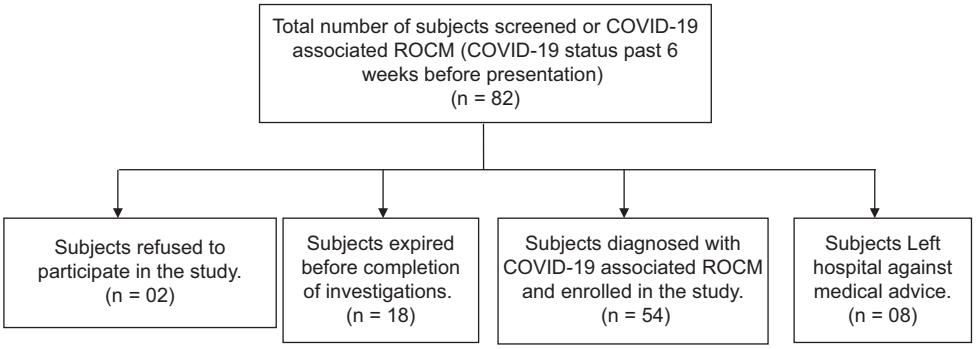

Figure 1: Flowchart showing screening and enrollment of subjects with COVID-19-associated rhino-orbito-cerebral mucormycosis.

Table 1: Sociodemographic and Clinical profile of subjects with COVID-19 associated ROCM.

S. no.	Parameter	CSS positive (n=15 subjects)	CSS negative (n=39 subjects)	*P* value
		Number (%)	Number (%)	
1	Age (years)	44±15	52±11	0.028
2	Gender (Males)	9 (60)	26 (67)	0.646
3	Covid Status			
	Positive	12 (80)	22 (56)	0.108
	Recovered/Suspect	03 (20)	17 (44)	0.108
4	ROCM Category			0.659
	Possible Mucormycosis	0 (0)	1 (3)	
	Probable Mucormycosis	04 (27)	15 (38)	
	Proven Mucormycosis	11 (73)	23 (59)	
5	Stage of ROCM			
	Stage 1	0 (0)	1 (2.5)	<0.005
	Stage 2	0 (0)	19 (49)	
	Stage 3	02 (13)	17 (44)	
	Stage 4	13 (87)	2 (5)	
6	Risk Factors and Co morbidities			
	Diabetes Mellitus	13 (87)	37 (95)	0.302
	Use of Corticosteroid	07 (47)	11 (28)	0.197
	Mehanical Ventilation or Supplemental Oxygen	01 (7)	6 (15)	0.393
	Primary or Secondary Immunodeficiency	01 (7)	8 (21)	0.221
	Chronic Kidney Disease	01 (7)	2 (5)	0.825
	Acute Kidney Injury/Tuberculosis/Coronary Artery disease.	00 (0)/00 (0)/00 (0)	2 (5)/2 (5)/2 (5)	0.371
	Past Stroke/hypertension	00 (0)/00 (0)	3 (8)/3 (8)	0.269
	Transplantation History	00 (0)	1 (3)	0.531
	Hepatitis B	01 (7)	0 (0)	0.104
	Hepatitis C	00 (0)	4 (10)	0.197
7	Duration of symptom onset (Mean±2S.D) days	12±7 (Median=10 days)	6±9 (Median=6 days)	0.005
8	KOH Smear positive	6 (40)	15 (38)	0.972
9	Biopsy positive	8 (53)	15 (38)	0.322
10	Culture positive	1 (7)	0 (0)	0.104
11	Antifungals used			
	Posaconazole	15 (100)	33 (85)	0.273
	Liposomal Amphotericin B	11 (73)	15 (38)	0.022
12	Surgical Treatment	9 (60)	3 (8)	0.001
13	Outcome			0.322
	Good: Discharge	8 (53)	15 (38)	
	Poor: Death/Referred/Lama	2 (13)/3 (20)/(13)	7 (18)/3 (8)/14 (36)	

to CSS-negative group including age of presentation, ocular, nasal, systemic features, cranial nerve involvement, and radiological findings in the orbit, paranasal sinuses, nose, and brain. Recognition of these features can help in early clinical prediction of spread of infection to the brain.

Patients can have ROCM during and even up to 3 months after recovery from COVID-19 and in this study, a higher number of CSS-positive group had active COVID-19 status.[20,21] Most of the subjects in CSS-positive group were proven and in advanced stages of ROCM as compared to CSS-negative group [Table 1]. The probable reason was aggressiveness of infection due to comorbidities and alterations in immunity during COVID-19.[9,18] As per our knowledge, the previous studies have not used the objective categorization and staging systems to assess the severity of CSS and ROCM.

CSS-positive group was significantly younger than CSS-negative group as seen in recent studies as compared to pre-COVID-19 era.[22,23] Males were affected more than females as consistent with the previous studies because COVID-19 and ROCM was more common in males, possibly due to outdoor exposure.[9,10,17,24] However, CSS due to non-infective causes was more commonly seen in females.[12] In our study, majority of the subjects were not vaccinated which emphasizes the role of COVID-19 vaccination to mitigate the risk of such

Table 2A: Clinical Features of subjects with COVID-19 associated ROCM.

Clinical features	CSS positive (n=15 subjects) number (%)	CSS negative (n=39 subjects) number (%)	*P* value
Nasal Clinical features	13 (87)	32 (82)	1.000
Nasal Stuffiness	6 (40)	12 (31)	0.519
Foul Smell	1 (7)	0 (0)	0.104
Epistaxis	0 (0)	2 (5)	0.371
Nasal Discharge	5 (33)	3 (8)	0.03
Nasal Mucosal Erythema, Inflammation, Purple or Blue Discoloration, White Ulcer, Ischemia, or Eschar	5 (33)	3 (8)	0.03
Regional Pain- Orbit, Paranasal Sinus or Dental Pain	11 (73)	26 (67)	0.637
Ocular Clinical Features	15 (100)	32 (82)	0.171
Proptosis	9 (60)	7 (18)	0.006
Loss of vision	11 (73)	19 (49)	0.103
Ophthalmoplegia	12 (80)	14 (28)	0.004
Ptosis	12 (80)	9 (23)	0.000
Eyelid Periocular or Facial Edema	15 (100)	30 (77)	0.125
Eyelid, Periocular, Facial Discoloration	6 (40)	9 (23)	0.02
Systemic and Cerebral Features	15 (100)	38 (97)	1.000
Fever	15 (100)	30 (77)	0.049
Headache	8 (53)	15 (38)	0.322
Facial Pain	8 (53)	22 (56)	0.839
Facial Paresthesias, Anesthesia	9 (60)	15 (38)	0.154
Facial Palsy	1 (7)	2 (5)	0.825
Altered Sensorium, Paralysis, Focal Seizures	5 (33)	7 (18)	0.223

Table 2B: Cranial nerve involvement in subjects with COVID-19 associated ROCM.

Cranial nerve	CSS positive subjects		CSS negative subjects		*P* value
	Unilateral number (%)	Bilateral number (%)	Unilateral number (%)	Bilateral number (%)	
Cranial nerve 2	9 (60)	2 (13)	17 (44)	2 (5)	0.103
Cranial nerve 3	9 (60)	4 (27)	11 (28)	2 (5)	0.000
Cranial nerve 4	8 (53)	2 (13)	9 (23)	1 (3)	0.005
Cranial nerve 5	8 (53)	1 (7)	12 (31)	4 (10)	0.210
Cranial nerve 6	8 (53)	4 (27)	17 (43)	1 (3)	0.025
Cranial nerve 7	1 (7)	0	2 (5)	1 (3)	0.897
Cranial nerve 9-12	1 (7)	0	2 (5)	1 (3)	0.897

coinfections. The duration of symptoms was significantly longer in CSS-positive group as seen previously.[9,10]

Common risk factors associated with CSS and ROCM were diabetes mellitus and use of corticosteroids as reported recently.[9,24] Intravenous corticosteroid used for immune modulation during COVID-19 causes hyperglycemia leading to impaired chemotaxis and phagocytosis of neutrophils. This along with excessive availability of free iron in diabetic ketoacidosis and decreased number of lymphocytes in coexisting COVID-19 increases the propensity to invasive ROCM. Other immunodeficiency states in this study group were primary or secondary immunodeficiency and organ transplantation similar to a recent study.[9]

CSS-positive group had increased features of ocular, nasal, and cerebral system involvement [Table 2]. Ocular features in CSS were more as compared to previously reported presentations with ROCM and concurrent COVID-19.[7,17,16] Eyelid, periocular and facial discoloration, ptosis, proptosis, and ophthalmoplegia were significantly more as compared to CSS-negative ROCM group which had been reported in a variable range.[10,24] These differences may be attributed to concurrent COVID-19 and variation in clinical presentations across these studies. Vision loss was seen in 73% subjects in our study as compared to previously reported 25–80% with ROCM.[7,25] Visual acuity was affected less in CSS due to non-infective etiology as compared to those with COVID-19-associated

Table 3: Neuroimaging features in subjects with COVID-19 associated ROCM.

Neuroimaging	CSS positive (n=15 subjects)	CSS negative (n=39 subjects)	P value
Imaging	**Number (%)**	**Number (%)**	
CT head and Orbit	10 (67)	29 (74)	0.736
MRI Brain and Orbit	12 (80)	18 (46)	0.025
Both CT & MRI brain	7 (47)	7 (18)	0.043
MRI Brain with Contrast	9 (60)	11 (28)	0.031
MR Venogram	3 (20)	0 (0)	0.005
3B. Neuroimaging Features			
1. Orbital			
Globe -Bony erosions	2(13)	3 (8)	0.522
Muscle infiltration	10 (67)	10 (26)	0.005
Fat infiltration	14 (93)	19 (49)	0.003
Optic Neuritis	4 (27)	2 (5)	0.024
Enhancement of orbital muscles	5 (33)	2 (5)	0.006
Enhancing soft tissue mass In Orbital Apex	9 (60)	2 (5)	0.000
Thickening and lateral displacement of inferior and medial rectus muscles.	10 (67)	9 (23)	0.003
Proptosis	9 (60)	8 (21)	0.005
Preseptal cellulitis	8 (53)	3 (7)	0.000
Prominent superior ophthalmic vein	1 (7)	1 (3)	0.475
2. Paranasal Sinuses			
Frontal sinus opacification and mucosal thickening	13 (87)	16 (41)	0.003
Maxillary sinus opacification and mucosal thickening	15 (100)	35 (90)	0.197
Ethmoid sinus opacification and mucosal thickening	15 (100)	35 (90)	0.197
Sphenoid sinus opacification and mucosal thickening	15 (100)	23 (59)	0.003
Cavernous sinus opacification and mucosal thickening	14 (93)	0 (0)	0.000
Infratemporal Fossa Infiltration	11 (73)	11 (28)	0.003
Air Fluid Level	9 (60)	7 (18)	0.002
Soft Tissue Infiltration of maxillary periantral fat planes	14 (93)	23 (59)	0.015
Bony Dehiscence	9 (60)	7 (18)	0.002
3. Nose			
Medial Concha infiltration	4 (27)	6 (15)	0.339
Inferior Concha infiltration	7 (47)	13 (33)	0.574
Inferior Turbinate Sign	2 (13)	2 (5)	0.495
Bony dehiscence	9 (60)	5 (13)	0.002
4. Brain			
Infarcts/Others(Abscesses, Edema)	6 (40)/6 (40)	11 (28)/11 (28)	0.403
5. Cavernous sinus-Direct Features			
Convexity of lateral wall of Cavernous Sinus	12 (80)	0 (0)	
Abnormal signal intensity on T1/T2 images.	13 (87)	0 (0)	
Filling defects in the cavernous sinus	9 (60)	0 (0)	
Cavernous internal carotid artery stenosis	7 (47)	0 (0)	

ROCM which may be attributed to perineural and perivascular spread of infection to optic nerve.[9,12]

ROCM spreads from nose and paranasal sinuses through lamina papyracea and orbital fissures to apex of orbit which acts as a window to cavernous sinus.[26] Our study showed that orbital apex lesion was more in CSS-positive as compared to CSS-negative group as had been seen in recent studies.[12,16] CSS-positive group had significant indirect radiological features including orbital and muscle infiltration, proptosis, pre-septal cellulitis, enhancement of orbital muscles, and optic neuritis which were more than that reported previously.[16] Clinicoradiological diagnosis of orbital apex syndrome can be useful in early recognition of the involvement of cavernous sinus in ROCM.

CSS-positive group had significant nasal discharge and mucosal inflammation as had been noted in a recent multicentric study from India.[9] Regional pain in paranasal sinus, orbit, or teeth in CSS may be due to fifth cranial nerve involvement or invasion of blood vessels in the bone by mucormycosis. In a recent study, dental pain was a common presentation of ROCM to oromaxillary facial surgeons during the COVID-19 pandemic.[7,24,27] Inferior turbinate sign and

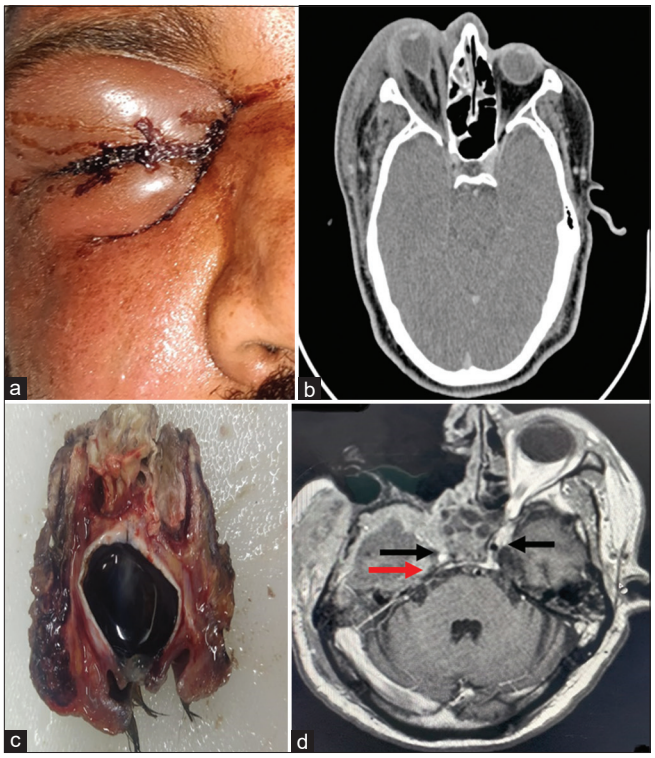

Figure 2: (a) Clinical picture of a patient with cavernous sinus syndrome with COVID-19-associated ROCM showing proptosis, ptosis, and ophthalmoplegia. (b) Axial view of CT head showing proptosis (red arrow), soft-tissue thickening in the right maxillary sinus (blue arrow), and soft-tissue thickening in the right temporoparietal region extending to scalp (yellow arrow). (c) Exenterated eye of patient with cavernous sinus syndrome with COVID-19-associated ROCM showing growth of mucormycosis (black arrow). (d) Axial view of contrast enhanced T1W MRI image of an exenterated eye showing non-enhancing right cavernous sinus (red arrow) and right cavernous ICA stenosis compared to the left side (black arrow).

nasal bone dehiscence were more as compared to the previous studies probably due to more aggressiveness of infections.[9]

Cavernous sinus was more likely to be involved with extension of infection to adjoining sphenoid sinus.[10] Other paranasal sinuses including maxillary and ethmoid sinus showed opacification and mucosal thickening similar to another study.[16] However, infiltration of periantral fat planes and air fluid level in maxillary sinus and infratemporal fossa with bony dehiscence was significantly more in CSS-positive group than that reported earlier.[16]

Systemic features including fever were seen in all CSS-positive group and were significantly more as compared to CSS-negative group. The previous studies have reported fever in less than one-third of subjects, possibly due to inclusion of non-infective causes of CSS.[7,12,24] Cerebral features such as headache, facial pain, paresthesias, and facial palsy were more in CSS-positive ROCM as compared to the previous studies.[24,10]

Most common cranial nerve involved in CSS-positive group were oculomotor, abducens, trochlear, and trigeminal nerve as opposed to another study where sixth nerve was followed by third, fourth, and fifth cranial nerve involvement [Table 2].[12] There is paucity of data regarding detailed description of involvement of cranial nerves in CSS associated with ROCM. Detailed neurological examination of cranial nerves is indispensable in diagnosing a clinical entity like CSS.

Due to higher risk of coinfection with ROCM in COVID-19, neuroimaging was performed more as compared to similar studies from India.[9,16] MRI brain is more sensitive for detecting ocular, paranasal sinuses, and brain involvement in ROCM. Whole cavernous sinus involvement was more common in contrast to a study from India which showed posterior cavernous sinus lesion, being most common in fungal infection.[12] The reason for this may be the aggressiveness of mucormycosis to involve the whole cavernous sinus with coexisting COVID-19 infection [Figure 2].

In our study, direct qualitative neuroimaging features in CSS-positive group included abnormal signal intensity and convexity of lateral wall of cavernous sinus as reported previously [Table 3].[14,15] Cavernous sinus thrombosis and internal carotid artery involvement were more as compared to the previous studies.[16,18,24] These vascular complications were due to spread of infection through adjoining orbits or sinuses or veins and hypercoagulable state with COVID-19.

Proven ROCM with microbiological evidence of mucormycosis in CSS-positive group was similar to a previous study.[24] Treatment of ROCM included antifungals and surgical intervention depending on clinical presentation, radiological extension, and tissue diagnosis. CSS-positive with proven ROCM was treated with intravenous liposomal or deoxycholate amphotericin-B similar to another study.[9] Treatment with oral posaconazole was given to all CSS (all categories of ROCM) due to high index of suspicion, coexistent comorbidities, and limited supply of Amphotericin B.

Surgical treatment was performed significantly more in CSS-positive group due to a higher number of subjects being advanced stages of proven ROCM. Although the literature shows that surgical intervention in ROCM with extension to CNS did not affect the survival but few studies have shown the positive effect on outcome.[9,28] The combined therapy of antifungal along with surgical intervention had better prognosis than either of them alone in ROCM but data specific to involvement of cavernous sinus are lacking.[9] Our study did not show significant difference in outcome across both the groups. The mortality rate of ROCM with orbital and cerebral involvement may be 30–90% but during the COVID-19 pandemic, it decreased to 14–40%.[9,22,29] The lower mortality rate in our study can be explained by high index of

suspicion and early diagnosis of ROCM and CSS in admitted patients during the second peak of COVID-19. In view of the prevailing COVID-19 pandemic with newer strains and rising fungal infections, further multicenter research involving a larger population is needed to understand the disease.

The limitations of the study are small sample size and a single-center experience. There were limited enrollment and follow-up of patients due to relocation of patients elsewhere possibly due to concurrent COVID-19 pandemic. Since it was a hospital-based study, subjects with milder disease may not have been admitted. The strength of study is prospective design and since the medical fraternity was novice to COVID-19, this study shows how COVID-19-associated ROCM unfolded itself to involve cavernous sinus and brain. Moreover, the study used objective clinicoradiological methods to categorize and stage both ROCM and CSS.

CONCLUSION

Incidence of CSS with COVID-19-associated ROCM was 28%. Extension of ROCM to CSS was more common in young males in advanced stages of proven ROCM associated with concurrent COVID-19. CSS-positive group had significant difference in clinicoradiological features involving orbit, nose, paranasal sinuses, and central nervous system as compared to CSS-negative group. This study highlights the need for further development and validation of an objective scoring system considering clinical and radiological features for early diagnosis of CSS in a larger sample of population across multicenter.

Ethical approval

The study was approved by the Institutional Ethics Committee-GGS/IEC/20/107.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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ANNEXURE

Annexure 1: Clinical features suggestive of ROCM with Concurrent COVID-19.[13]

Nasal features	Ocular features	Systemic and cerebral features
Nasal Stuffiness	Proptosis	Fever
Foul Smell	Loss of vision	Headache
Epistaxis	Ophthalmoplegia	Facial Pain
Nasal Discharge	Ptosis	Facial Paresthesia, Anesthesia
Nasal Mucosal Erythema, Inflammation, Purple or Blue Discoloration, White Ulcer, Ischemia, or Eschar	Eyelid Periocular or Facial Edema	Facial Palsy
Regional Pain- Orbit, Paranasal Sinus or Dental Pain	Eyelid, Periocular, Facial Discoloration	Altered Sensorium, Paralysis, Focal Seizures

Annexure 2: Proposed qualitative radiological features of cavernous sinus syndrome.

Direct radiological features	Indirect radiological features		
Cavernous sinus	**Orbit**	**Sinus**	**Nose**
1. Convexity of Lateral Wall of Cavernous Sinus 2. Abnormal Signal Intensity on T1/T2 3. Filling Defects in Cavernous Sinus 4. Cavernous ICA stenosis	1. Globe -Bony Erosions 2. Muscle Infiltration 3. Fat Infiltration 4. Optic Neuritis 5. Enhancement of Orbital Muscles 6. Enhancing Soft Tissue Mass In Orbital Apex 7. Thickening and Lateral Displacement of Inferior and Medial Rectus 8. Proptosis 9. Preseptal Cellulitis 10. Prominent Superior Ophthalmic Vein	1. Sinus Opacification and Mucosal Thickening in : Frontal , Maxillary, Ethmoid , Sphenoid, Cavernous sinus 2. Infratemporal Fossa Infiltration 3.Air Fluid Level 4. Soft Tissue Infiltration of Maxillary Periantral Fat Planes 5. Bony Dehiscence	1.Medial Concha Infiltration 2.Inferior Concha Infiltration 3.Inferior Turbinate Sign 4. Bony Dehiscence

Annexure 3: Categories of CSS using Ishikawa classification.[14,12]

Anterior CSS	Middle CSS	Posterior CSS	Whole CSS
Optic neuropathy or isolated palsy of superior or inferior branch of Oculomotor nerve, regardless of other ocular motor nerves or Ophthalmic nerve involvement	Concurrent oculomotor nerve and ophthalmic nerve involvement	Involving the maxillary nerve or abducens nerve with Horner's Syndrome	Involving both optic nerve and maxillary nerve in addition to ocular motor nerves and ophthalmic nerve involvement