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Complete and incomplete lower motor neuron facial palsy in post-COVID-19 mucormycosis

Manushree Gautam, Meenal Soni, Vijay Bhaisare, Preeti Rawat, Shweta Walia, Neetu Kori

Purpose: To study facial nerve palsy (FNP) in post-COVID-19-mucormycosis patients and its ocular complications, report different presentations of FNP in such patients, and propose its etiopathogenesis based on presentation and clinico-radiologic localization. **Methods:** A prospective cohort study was carried out in patients of post-COVID-19-mucormycosis who presented at our tertiary center, over a period of 3 months. Motor and sensory examination of the facial nerve was done to diagnose FNP and localize the lesion clinically. Slit-lamp examination was done for grading corneal involvement. MRI brain, orbit, and paranasal sinuses (PNS) with contrast were studied to find involvement along the facial nerve. It was assessed whether this site of lesion corresponded with clinical localization. Data were analyzed using the percentage of total cases and Fisher's test. **Results:** A total of 300 patients with post-COVID-19 mucormycosis were examined, of which 30 (10%) patients were found to have FNP. All were lower motor neuron (LMN) type and were associated with corneal complications. The most common site clinically was distal to the chorda tympani (66.66%) and radiologically was infratemporal (IT) fossa (63.4%). The clinical localization significantly correlated with the radiological findings (P = 0.012). Twenty percent of patients showed incomplete involvement of facial muscles. **Conclusion:** FNP was found to be of LMN type. The most common site of insult was IT fossa. There was a good clinico-radiological correspondence of lesions. Isolated lesions were also found along the peripheral nerve course, presenting as incomplete facial palsy. Recognition of FNP in post-COVID-19 mucormycosis, in all its variable forms, is important to manage corneal complications.

Key words: Corneal complications, facial palsy, incomplete palsy, isolated orbicularis weakness, LMN palsy, post-COVID-19 mucormycosis

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Mucormycosis is a rare yet serious angioinvasive opportunistic infection caused by a group of fungi of order Mucorales. It mainly affects immunocompromised people. Risk factors include diabetes (especially diabetic ketoacidosis), solid organ or hematopoietic stem cell transplantation, neutropenia, long-term systemic corticosteroid use, iron overload, and malignancy.[1] Depending on the site affected, the disease may manifest in six different forms: rhinocerebral, orbital, pulmonary, cutaneous, gastrointestinal, and disseminated. Rhinoorbital cerebral mucormycosis (ROCM) is the commonest type accounting for 30–50% of cases.[2] India has reported a recent surge in mucormycosis cases post-COVID-19.[3] The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, and steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins), and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background co-morbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.[4]

Facial nerve palsy (FNP) has been documented as a neurological manifestation associated with COVID-19 proposed to be caused by microthrombi, direct viral damage, or an autoimmune reaction toward the nerve.[5] The frequency of FNP in ROCM has been reported from 11%[2] to 40%.[6] Other than direct inflammation by mucormycosis in the orbit, FNP also causes significant ocular complications in these patients.[2] Only a few reports discuss the etiopathogenesis of FNP and its site of lesion in ROCM.[7]

We studied FNP in patients with ROCM and its ocular complications. We found different presentations of FNP including complete and incomplete lower motor neuron (LMN) palsy. We propose its etiopathogenesis based on the presentation and localization of lesion clinically as well as radiologically.

Methods

This prospective cohort study was carried out in patients with mucormycosis who presented at our tertiary care center over a period of 3 months. A case of mucormycosis was defined as one that had clinical and radiological features consistent with mucormycosis along with the demonstration of the fungus in tissues (broad, aseptate, or pauci-septate hyphae

Department of Ophthalmology, MGM Medical College Indore, Madhya Pradesh, India

Correspondence to: Dr. Meenal Soni, MGM Girls Hostel, Near MYH Hospital, Residency Area, Indore - 452 001, Madhya Pradesh, India. E-mail: msoni26895@gmail.com

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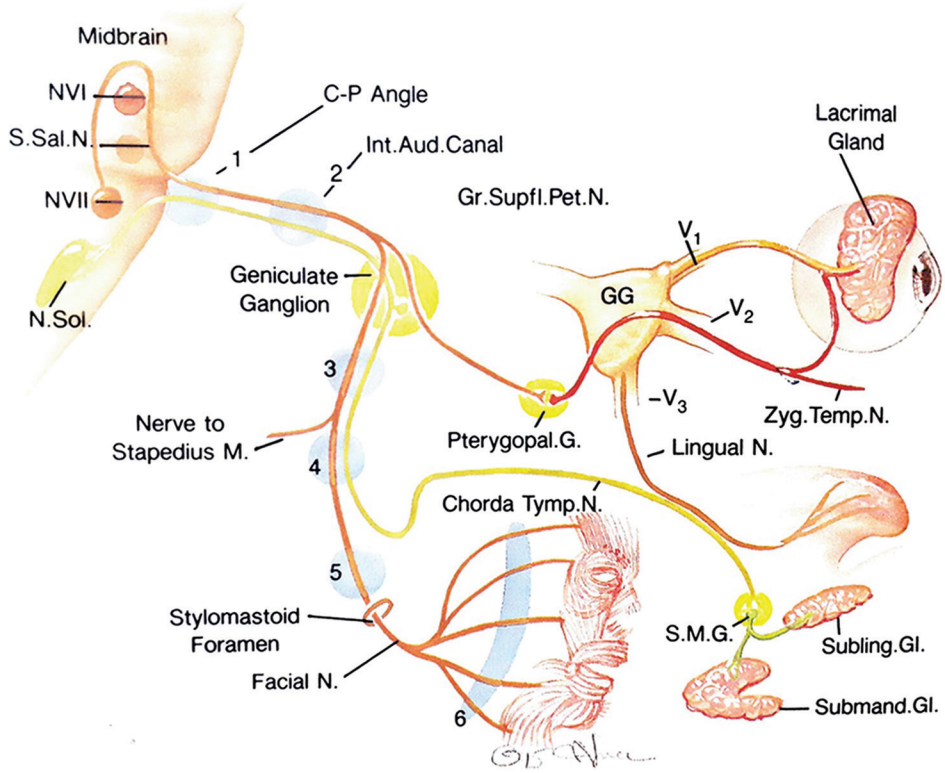

Figure 1: Showing clinical site localization of facial nerve palsy

with wide-angle branching and evidence of tissue invasion) via KOH mount/culture/histopathological examination. The clinical features considered were nasal congestion, toothache/loosening of tooth, headache/retro-orbital pain, facial swelling, erythema, ptosis and/or proptosis, facial numbness, deviation, and focal neuro deficits (hemiparesis, paraparesis, and extraocular muscle involvement), developing recently in a background of COVID-19 disease in patients who had risk factors such as diabetes, steroid use. COVID-19 disease was documented by positive reverse transcription-polymerase chain reaction (RT-PCR) within the last 3 months. All patients were now negative on COVID-19 RT-PCR. Radiological criteria for the diagnosis of mucormycosis were dependent on the presence of features of invasive fungal disease such as bony erosion, extraocular muscle, vascular, and soft tissue invasion. A thorough clinical history, ocular examination, and examination of cranial nerves from third to eighth (due to close proximity of nerve courses) were done for each patient.

Facial nerve examination was carried out in terms of its motor and sensory functions to diagnose FNP. At rest, any asymmetry of facial expression, presence of ectropion, absence of nasolabial fold, and facial deviation were noted. Various muscle groups were examined by asking the patient to wrinkle the forehead for frontalis action by temporal branch; forcibly close the eyes for orbicularis by zygomatic; smile and puff out their cheeks, show teeth for buccinator and zygomaticus by buccal branches; forcefully depress and draw inferior lip laterally by marginal mandibular and tense the skin of the anterior neck for the cervical branch to platysma. Taste sensations of the anterior two-thirds of the tongue on each side were tested by putting drops of sweet and salty water on the tongue and asking the patient whether and what taste sensation was appreciated.[8]

Facial swelling confounded the absence of the nasolabial fold; however, the function of the buccal branch could be assessed in these patients by puffing. In patients with co-existing proptosis, the presence of ectropion, and closure of lids could not be assessed, thus the function of orbicularis oculi was masked. In these patients for the ease of study, orbicularis was considered involved if both frontalis and buccinators were involved.

Facial nerve lesion was localized clinically and labeled, as shown in the picture: [Fig. 1].[8]

Site 1, that is, lesion at cerebellopontine (CP) angle where all functions of the facial nerve are lost with adjacent brain stem and other cranial nerve findings; site 2 includes lesion in internal auditory canal (IAC) with features same as site 1 but without brain stem and other cranial nerve findings; site 3 lesion between geniculate ganglion and nerve to the stapedius has loss of taste sensation, altered hearing, and impaired salivation; site 4 includes lesion between nerve to the stapedius and chorda tympani with loss of taste sensation and impaired salivation; site 5 with lesion distal to the chorda tympani causing isolated paralysis of facial muscles and site 6 with lesion distal to branching of the motor trunk seventh nerve causing paralysis/weakness of smaller groups of facial muscles.

Another cranial nerve examination was carried out as follows[8]: for cranial nerves III, IV, and VI extraocular movements in all cardinal gazes were examined; for cranial nerve V, sensations over the cornea and different facial areas of distribution according to its subdivisions were tested and

for cranial nerve VIII, any symptoms or signs of nystagmus, vertigo, ataxia, and hearing impairment were tested.

Ocular examination was carried out in terms of anterior segment examination under torchlight and slit-lamp, after which corneal involvement was graded as follows[9]: grade I means punctate epithelial erosions (PEEs) involving the inferior third of the corneal surface; grade II were those with PEEs involving > an inferior third of the corneal surface; grade III as a macro epithelial defect (MED); grade IV with stromal whitening in the presence of epithelial defect (SWED); grade V were those with stromal scarring and grade VI were patients with microbial keratitis.

Grade I and II patients were managed medically with lubricants and taping, those with grade III and above underwent tarsorrhaphy.

All subjects on admission underwent 3 T magnetic resonance imaging (MRI) of the brain, orbits, and paranasal sinuses (PNS), both plain (T1, T2/T2 fluid attenuation inversion recovery sequence [FLAI]), T2 fat suppression) and contrast studies. MRI brain, orbit, and PNS with contrast were studied to find possible involvement along the pathway of the facial nerve. It was assessed whether this site of the lesion corresponded with clinical localization.

Data were analyzed using the percentage of total cases and Fisher's test as applicable.

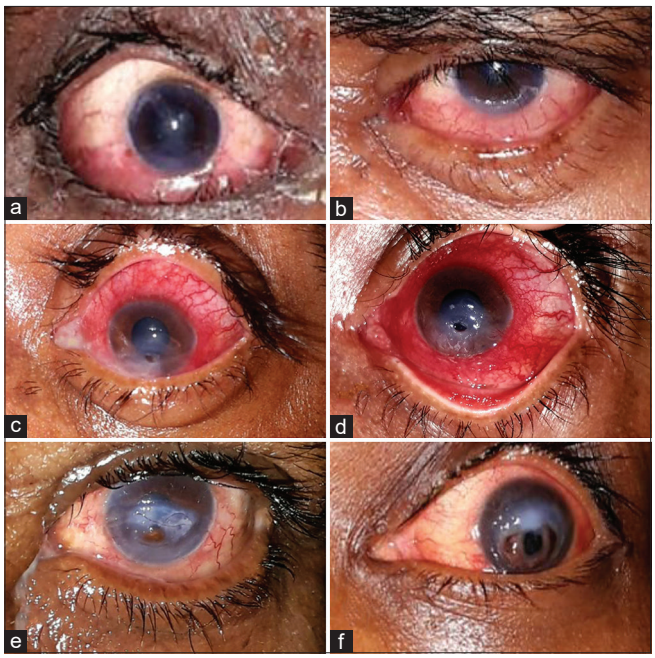

Figure 2: Showing corneal involvement in post-COVID-19 ROCM FNP patients. (a and b) Grade III corneal involvement (macro epithelial defect). (c) Grade VI corneal involvement (microbial keratitis). (d) Grade IV corneal involvement (stromal whitening in the presence of epithelial defect). (e) Grade IV corneal involvement with descemetocele formation. (f) Corneal melting with pseudocornea formation

Results

A total of 300 patients with post-COVID-19 mucormycosis were examined, of which 30 (10%) patients were found to have FNP. All 30 patients had hyperglycemia on admission, with 14 known cases and 16 newly diagnosed cases of diabetes. All newly diagnosed diabetic patients had a history of steroid use. In total, 20 patients had a history of steroid use, the duration was more than 2 weeks in all of them. There was a history of remdesivir use in all patients. Twenty-seven patients with FNP had a rhino-orbital or cerebral stage of mucormycosis, whereas three patients had only rhino nasal involvement. Of the 30 patients, 24 were male and 6 were female (M: F: 2.3:1) and age ranging from 28–69 years (median age: 45 years). All were LMN type and were associated with some form of ocular complication in the ipsilateral eye only. Patients with corneal involvement up to grade II were 16 (53.33%) and those with grade III and above were 14 (46.66%). One patient had microbial keratitis, which responded well to empirical therapy with topical moxifloxacin eye drops 2 hourly and chloramphenicol eye ointment twice a day and median tarsorrhaphy. The number of patients requiring surgical intervention with tarsorrhaphy was 14 (46.66%) [Fig. 2].

Twenty-two patients also had fifth nerve involvement. Corneal involvement did not correlate with coexisting fifth nerve involvement (*P*-value: 0.325).

Clinically, none of the patients showed involvement at sites 1, 2, and 3.

The most common site clinically was site 5, that is, distal to chorda tympani (20 patients, 66.66%) and radiologically was infratemporal (IT) fossa (19 patients, 63.4%) [Table 1] and [Fig. 3].

Six out of 30 patients (20%) showed incomplete involvement of facial muscles; therefore, the clinical site of localization was at site 6. Out of these; two patients had isolated orbicularis involvement; three patients had involvement of frontalis,

Table 1: The distribution of clinical and radiological site of lesion in LMN palsy was as follows

Site of lesion clinically	No. of patients with percentage	Site of the lesion in MRI	Percentage out of total (%)
4	4 (13.33%)	Otomastoiditis-1	3.3
		Infratemporal fossa-3	10
5	20 (66.66%)	Infratemporal fossa-16	53.4
		Other:	6.7
		Pterygopalatine fossa-2	6.7
		Masticator space-2	
6	6 (20%)	Pre maxillary and	13.3
		maxillary-4	3.3
		Masticator space-1	3.3
		Buccomassetric region-1	

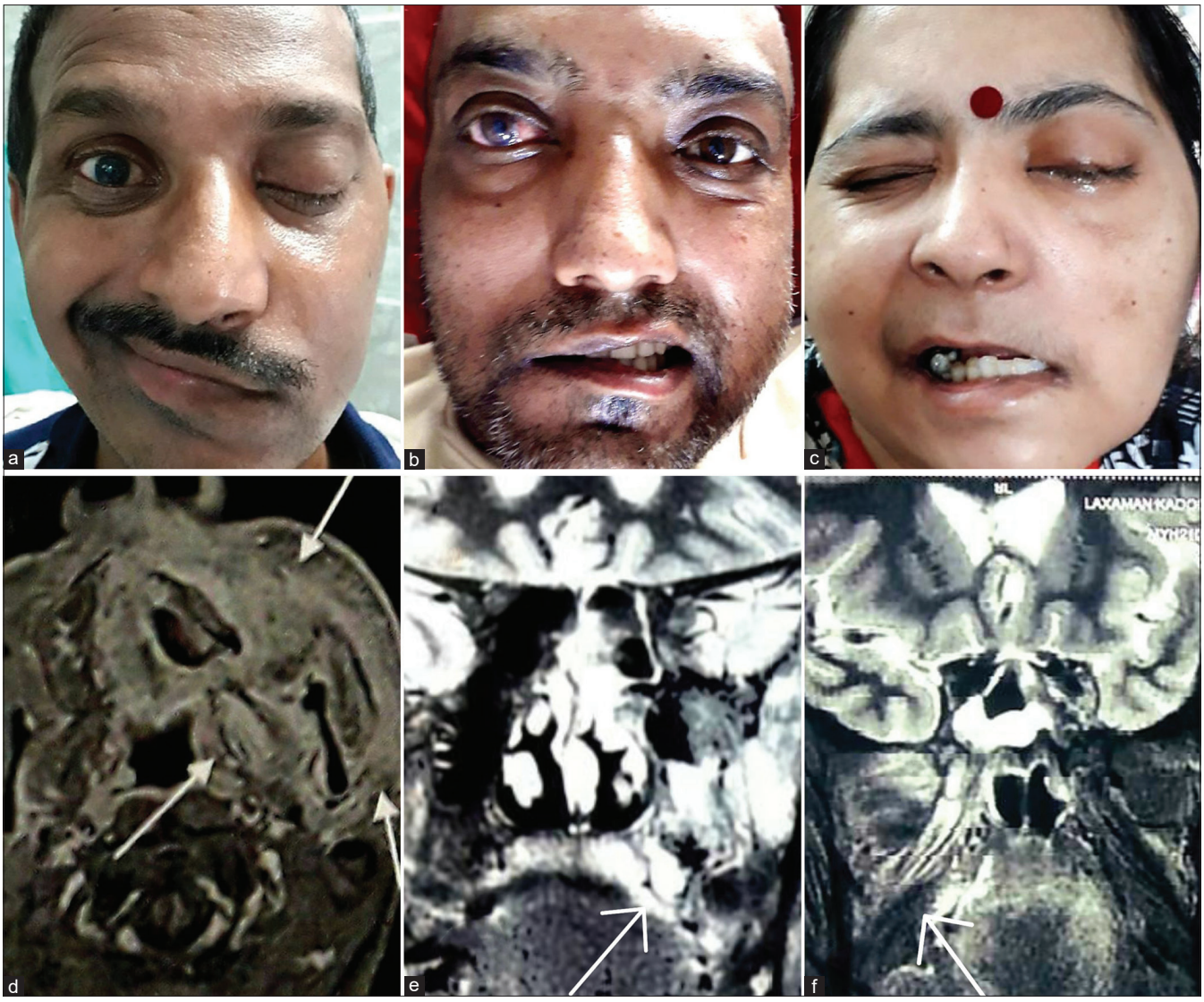

Figure 3: Showing complete facial nerve palsy LMN type and the associated radiological findings. (a and c) Left-sided complete LMN palsy associated with third nerve palsy. (b) Right-sided complete LMN palsy. (d) MRI paranasal sinuses with contrast (arrows) showing enhancing inflammatory lesions in the left infratemporal fossa. (e and f) MRI brain orbit and paranasal sinuses with contrast (arrows), showing enhancing inflammatory lesions in the infratemporal fossa, left and right, respectively

Table 2: Correlation of clinical localization with MRI findings was as follows

Clinical site	4	5	6
Lesion correlating with MRI	1	18	6
Lesion not correlating with MRI	3	2	0

or, and elevators of the upper lip with sparing of depressors and platysma; one patient had involvement of orbicularis and elevators with sparing of frontalis, depressors, and platysma [Fig. 4] and [Table 2].

The clinical localization of FNP in mucor patients significantly correlated with the radiological findings with a *P* value of 0.0127.

All patients are under observation and have been followed for a minimum of 2 months. FNP neither evolved nor regressed in any of the patients. Corneal condition improved in all patients after medical management and tarsorrhaphy.

Discussion

In our study, the frequency of FNP in patients of post-COVID-19 mucormycosis was found to be 10%, earlier studies have reported 11% cases in ROCM in diabetics[2] and 40% cases in post-COVID-19 ROCM.[6] In our study, all 30 patients had hyperglycemia on admission, with 14 known cases and 16 newly diagnosed cases of diabetes. All newly diagnosed diabetic patients had a history of steroid use and hence could be steroid-induced. Although the exact mechanism of facial nerve involvement in post-COVID-19 mucormycosis is unknown, Bakshi suggested that if the infection spread through the pterygopalatine fossa and reaches the infratemporal (IT) fossa, it may affect the facial nerve as it exits the stylomastoid foramen.[3] The involvement of pterygopalatine fossa has been reported by some authors as a route of the spread of mucormycosis to the facial nerve. This fossa is also considered to be a reservoir of mucor from where it spreads to the retroglobal space of orbit and infratemporal space. Thus, the

Figure 4: Showing incomplete facial nerve palsy LMN type. (a-c) Patients with involvement of frontalis, orbicularis, and elevators of the upper lip with sparing of depressors of lower lip and platysma on right, left, and left sides, respectively. (d) Patient with involvement of orbicularis and elevators of the upper lip with sparing of frontalis, depressors, and platysma. (e) Patient with isolated orbicularis involvement, ectropion of lower lid seen. (f) Patient with isolated orbicularis involvement with tarsorrhaphy

infection can spread to the inferior orbital fissure, orbital apex, and infratemporal fossa.[10]

In our study, all patients of FNP had an LMN type of lesion. Dubey *et al*.[6] also found that LMN outnumbered upper motor neuron (UMN) type of facial palsy in post-COVID-19 ROCM with three UMN and 19 LMN types. Upon clinical localization, 20 patients had lesion at site 5, that is, distal to chorda tympani, they had complete paralysis of ipsilateral facial muscles, which corresponded to a lesion at IT fossa on MRI in 16 patients and pterygopalatine fossa in 2 patients, respectively; however, two patients had lesion only in the masticator space, which does not explain paralysis of all facial muscles. Four patients clinically had lesions at site 4, that is, between the nerve to the stapedius and chorda tympani explained on MRI by otomastoiditis in one patient, whereas three had lesions at IT fossa, which did not explain the loss of taste. All six patients with a lesion at site 6, distal to branching of the motor trunk of seventh nerve, presented as incomplete LMN palsy and showed a corresponding isolated lesion on MRI.

Therefore, on correlating clinical localization with the MRI findings, only five lesions could not be explained for which we propose perineural invasion as the possible mechanism for such presentation. Mucormycosis can spread some distance from its primary focus, along peripheral nerves, a phenomenon that can be identified using contrast-enhanced MRI.[11] Moreover, the perineural invasion was associated with angio-invasion, nerve microenvironment, and neurotropic factors secretion, playing a pivotal role in the pathogenesis of perineural invasion.[12]

Amongst patients with incomplete involvement of facial muscles, two patients had isolated orbiculars oculi involvement and presented with ocular pain, watering, and redness. On examination, they showed lagophthalmos and grade 1 ectropion with macroepithelial defects in the cornea (grade 3); both these patients had rhinonasal mucormycosis with no orbital involvement on MRI and were taken for tarsorrhaphy. Three patients had involvement of frontalis, orbicularis, and elevators of the upper lip with sparing of depressors

and platysma; out of these two patients had lagophthalmos with grade 1 ectropion, conjunctival congestion, and grade 4 corneal involvement, one had co-existing third nerve palsy thus restriction of extraocular movements and ptosis, this patient had inferior conjunctival congestion with grade 1 corneal changes. One patient had involvement of orbicularis and elevators with sparing of the frontalis, depressors, and platysma; this patient had facial deviation with sparing of frontalis and hence mimicked UMN palsy; however, careful examination showed sparing of lower facial muscles, which also correlated with MRI.

Thus, FNP in post-COVID-19-ROCM had varied and differential presentations. This could be due to most peripheral involvement by direct invasion of mucormycosis or due to vasa nervorum angio-invasion by mucor causing infarction of facial nerve at that level and also due to perineural spread away from the main source.

Isolated orbicularis oculi weakness is a rare condition and has been reported with leprosy[13] and as idiopathic.[14] We suggest post-COVID-19 ROCM as a differential for this condition.

Conjunctival congestion and variable corneal involvement were found in all our patients, the severity of which did not correlate with coexisting sensory/fifth nerve involvement, unlike previous studies.[15,16] All cases responded well to tarsorrhaphy. Thus recognition of FNP in post-COVID-19 mucormycosis, in all its various forms is important to manage ocular complications.

Conclusion

FNP is a common cranial neuropathy in post-COVID-19 ROCM and can cause severe corneal complications. It was found to be of LMN type. The most common site of insult was IT fossa. There was a good clinico-radiological correspondence of lesions. Isolated lesions were also found along the peripheral nerve course, presenting as incomplete facial palsy. Recognition of FNP in post-COVID-19 mucormycosis, in all its variable forms, is important to manage ocular complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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