

Invasive Fungal Sinusitis in Patients With Coronavirus Disease 2019 Seen in South India

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Background: Coronavirus disease 2019 (COVID-19) has a vast array of presentations and associations with neuro-ophthalmic diseases. There has been a recent surge in ophthalmic manifestations secondary to fungal sinus infections in India especially in diabetic patients who were given systemic steroids. We present our COVID-19–related cranial neuropathies presenting in our clinic.

Methods: This is a retrospective case series of 10 patients affected with COVID-19 disease and who presented with cranial nerve palsies at the neuro-ophthalmic department of a tertiary eye care hospital in South India. An analysis of electronic medical records data was performed, including their comorbidities, symptoms, cranial nerves involved, ocular and neuroimaging findings, site of lesion, etiology, and prognosis.

Results: Most of the patients (7 of 10) presented with multiple cranial nerve palsies (MCNP) with poor visual acuity. 2 of the 10 cases succumbed to death due to the intracranial involvement. All MCNP cases had uncontrolled diabetes with a history of systemic steroids, and neuroimaging of these cases showed sinusitis of varying severity most of which were suggestive of fungal invasive type.

Conclusion: Our study emphasizes the need to screen for fungal involvement in COVID-19 cases presenting with MCNP especially on diabetic patients on systemic steroids so that an early diagnosis may reduce visual loss and mortality. Physicians treating COVID-19 cases need to be aware of this dreadful complication.

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On March 11, 2020, the World Health Organization declared the novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 as a pandemic (1). The disease produces symptoms ranging from asymptomatic disease to fatal

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acute respiratory distress syndrome (ARDS) and death (2). Disease severity may vary depending on the patient's comorbidities and state of the immune system (3). Ophthalmic manifestations include conjunctivitis, keratoconjunctivitis, anterior uveitis, retinitis, chorioretinal disease, and multiple neuro-ophthalmic symptoms (4). These neuro-ophthalmological symptoms and signs can appear isolated or associated with neurological syndromes (5) and is now well-known. The use of systemic steroids is posing new challenges such as emergence of opportunistic fungal infections especially in patients who are diabetic or are immunocompromised from other causes. There has been a recent surge in mucormycosis in India after the inadvertent use of systemic steroids in the management of COVID-19 (6).

The objective of our study was to analyze a series of 10 patients with reverse transcription polymerase chain reaction (RT-PCR)–positive COVID-19 who presented to us with cranial nerve palsies. None of these patients had severe form of ARDS and needing intensive care unit (ICU) admission. Fungal etiology was in most cases who were diabetic and on systemic steroids. We attempt to highlight the need to be vigilant and continue neurological and cognitive monitoring of all COVID-19 cases especially those who are diabetic and on systemic steroids.

METHODS

A retrospective study of a case series of 10 consecutive patients, who presented to a neuro-ophthalmology department at a tertiary eye care hospital in South India, 7 from September to November 2020 (first COVID-19 wave) and 3 in May 2021 (second COVID-19 wave). All the cases presented with diplopia and/or drooping of an eyelid and were RT-PCR–proven for COVID-19 infection. Patients with diplopia (from ischemic/traumatic causes) and those who were COVID-19 negative were excluded from this study. For all the patients detailed history, refraction, slitlamp, neuro-ophthalmologic, and fundus examination were performed. Neuroimaging was performed for all. Data were collected from our electronic medical records and retrospectively evaluated for these patients. Informed consent

was obtained from all the patients, and the study was approved by the institutional review board.

RESULTS

Our case series had 7 patients who presented to us during the first wave of the pandemic (September to November 2020). For next 5 months, we did not see such cases but in the first half of May 2021 (second wave), 3 more patients presented to us. Of our case series of 10 patients, 7 were between ages 45 and 55 years and others were aged 69 years, 71 years, and 33 years. 80% (8 of 10) of our cases were male patients. Three cases presented with diplopia and had isolated nerve palsy, 2 with sixth nerve, and 1 with superior division of third nerve palsy. The remaining 7 patients had multiple cranial nerve palsies and in whom drooping of the eyelid and pain was the main presenting complaint. All the 3 patients with isolated nerve palsies had no systemic illnesses and had normal vision. However, in patients with multiple cranial nerve palsies, all had uncontrolled diabetes and 5 had a history of taking systemic steroids (Table 1). The posterior segment of 2 patients had central artery occlusion, 2 had optic atrophy, and 1 had disc edema. Six of our patients gave a history of hospital admission and oral antiviral and dexamethasone administration before the neuro-ophthalmic manifestation. However, none of the patients had a history of ICU admission or artificial ventilation support. All other patients were diagnosed COVID-19—positive after or simultaneously with neuro-ophthalmological presentation and gave no history of prior diagnosis.

MRI of the brain and orbit with contrast of 8 patients showed variable severity of sinusitis from mild (confined to sinus) to invasive fungal sinusitis (orbital and intracranial extension). Six were diagnosed as fungal etiology on neuroimaging findings and all were diabetic, and 5 of the 6 cases had received systemic steroids. Only 1 was biopsy-proved mucormycosis (2 succumbed to death within 2 days, and the other 2 did not follow-up with the biopsy report). Two patients had normal neuroimaging. Reports of 2 patients with chest imaging were available, which were normal. Patients with mononeuropathy had good prognosis. In 5 patients with multiple cranial nerve palsies who had undergone neurologist and ear, nose, and throat (ENT) specialists' intervention, the extraocular movements showed improvement but had residual visual deficit. Unfortunately, 2 patients who had intracranial involvement succumbed to death within 2 days of presenting to us.

CONCLUSIONS

Our study showed that although COVID-19 can cause isolated nerve palsy (3 of 10 patients), it can also indirectly cause multiple cranial nerve palsies (7 of 10 patients) secondary to invasive fungal sinusitis because of the inadvertent use of systemic steroids in diabetic or immunocompromised patients. In our series, 6 patients had fungal etiology with neuroimaging showing sinusitis of varying severity and

all were diabetic. Five of these 6 cases were given systemic steroids. The cause of sinusitis can be attributed to the administration of steroids in diabetics leading to increase in blood sugars which leads to an immunocompromised state causing opportunistic infections, such as mucormycosis, to invade the sinuses. Interestingly, none of our cases had any severe form of COVID, and none were admitted in the ICU or on ventilator for ARDS. Recently, there has been an alarming trend of mucormycosis seen in patients with COVID-19 in India (7) and has also been reported in various parts of the world (8). This is probably related to the steroid usage during the COVID-19 treatment, leading to high morbidity (9).

Physiopathology of neurological involvement in COVID-19 is not yet fully understood. The main possibilities include direct viral neurotropism and indirect immunologic and neurovascular effects (10). Three main putative mechanisms of neurological injury have been proposed—direct viral central nervous system invasion, endothelial dysfunction, and a neurotoxic effect from excessive inflammation and cytokine release (11). One theory suggests that the coronavirus is a neurotrophic and neuroinvasive virus and that hypogeusia and anosmia are manifestations of the peripheral nervous systems' involvement, and hence, this maybe a way of infection into the nervous system. Because the central and peripheral nervous system can be affected, neuro-ophthalmic manifestations can occur (5).

Several case reports and articles document the neuro-ophthalmic manifestations of COVID-19 (increased incidence of papilledema, ophthalmoplegia, isolated cranial nerve palsies, and optic neuritis, to name a few). However, in our case series of 10 patients, we attempt to analyze only COVID-19–related cranial nerve palsies. Most of these patients presented to us with cranial nerve palsies after the onset of COVID-19 symptoms. The neurological manifestations are seen in middle-aged patients. Most of the patients with multiple cranial nerve palsies on presentation had poor vision and also had poor visual prognosis. Unfortunately, because of late presentation and intracranial spread, it led to the mortality in 2 patients. Multiple cranial nerve palsies were seen in patients with comorbidities; uncontrolled diabetes secondary to systemic steroid administration was a major precursor in our study.

New treatment protocols have been put into place to combat this new crisis in India to reduce the mortality. Because these cases presented quite late to us, physicians should be cautioned in administering steroids in diabetic patients with close blood sugar monitoring and be alert in picking up the clinical findings earlier and work with the team of ENT surgeons, neurologists, pulmonologists, and radiologists, thus trying to reduce vision loss and mortality. We attempt to highlight the benefit of having ophthalmologists, working alongside, as a part of the multidisciplinary team at the frontline when patients with COVID-19

TABLE 1. Subject demographics and outcome

Case No.	Age/ Sex Eye	Presenting Symptoms	Duration	BCVA & CN	COVID-19 Treatment Details	Comorbidity	MRI Findings	Etiology on MRI	Final Outcome
1	49/ OD M	Diplopia Headache URTI	5 days	20/ 20 VI	Home quarantine	Nil	Bilateral maxillary sinusitis	Inflammatory	Full recovery
2	69/ OS M	Diplopia lid drooping	2 months	20/ 40 III & VI	Hospital admission (AZ/Hcq/ FL/dexa)	DM	Acute invasive fungal sinusitis	Fungal	ENT & neurologist referral Full recovery
3	49/ OD M	Lid drooping vision loss	7 days	No PL I to VI	Hospital admission (PH/cef)	DM	Cerebritis, CST, invasive fungal sinusitis	Fungal	Died
4	53/ OS F	Vision loss anosmia	20 days	PL + II, III, VI	No steroids	DM & HT	Inflammatory soft tissue thickening at the orbital apex	Inflammatory	Treated with IVMP & oral steroids. Recovered with visual deficit
5	55/ OS M	Diplopia	1 month	20/ 20 VI	Home quarantine Was on antivirals and oral steroids	Nil	Normal	Inflammatory	Complete recovery
6	50/ OS M	Lid drooping Headache Anosmia	1 month	No PL I to VI	Hospital admission with steroids	DM	Infective fungal sinusitis with cavernous sinus extension, mastoiditis, intracranial extension to left middle cranial fossa	Fungal	Died
7	46/ OS M	Vision loss Pain on eye movements Proptosis	2 weeks	HM II, III	Hospital admission with steroids	DM	Acute infarcts in the left frontal & parietal lobes Soft tissue thickening at the level of the orbital apex, superior orbital fissure, & cavernous sinus with significant sinusitis	Fungal ischemic infarcts	Neurologist + ENT referral No follow-up
8	53/ OS M	Lid drooping Pain & swelling	3 weeks	II to VI	Hospital admission with doxy, ivermectin, remdisivir, dexa	DM	Invasive fungal sinusitis, left perineuritis with preseptal cellulitis Intracranial abscess, pachymeningitis, SOV thrombosis	Fungal	ENT & neurologist referral EOM recovered with visual deficit
9	71/ OS M	Lid drooping Fever	1 week	20/ 200 II to V	Hospital admission with AZ, ivermectin, doxy, dexa	DM	Bilateral ethmoidal, frontal & maxillary sinusitis with rarefaction of left lamina papyrea, orbital apex + cellulitis	Infective— fungal (mucormycosis confirmed)	Partial recovery
10	33/ OD F	Lid drooping	5 days	20/ 20 III	Home quarantine AZ, ivermectin	Nil	Normal	Inflammatory	Complete recovery

M, male; F, female; BCVA, best-corrected visual acuity; CN, cranial nerve affected; AZ, azithromycin; HCQ, hydroxychloroquine; FL, favipiravir; dexa, dexamethasone; ENT, ear, nose, and throat specialists; DM, diabetes mellitus; ENT, otolaryngologist; PH, phenytoin; cef, cefotaxime; PL, perception of light; CST, cavernous sinus thrombosis; HT, hypertension; IVMP, intravenous methyl prednisolone; HM, hand movements; doxy, doxycycline; SOV, superior orbital vein.

present with cranial neuropathies. This might help to trend carefully, use steroids judiciously, diagnose the early signs, and prevent serious complications.

There are several limitations to our study. One is that this is a small sample of 10 patients. The treatment protocol for patients with COVID-19 varies from hospital to hospital. Most of our patients had not undergone chest computed tomography (CT) imaging because they were asymptomatic, had mild symptoms, or were under home quarantine. If CT scans were available, we could probably clinically correlate the incidence of neuro-ophthalmological involvement and respiratory manifestations of the patient. Moreover, nasal endoscopy and biopsy reports are lacking to determine the exact pathogen of sinusitis, and fungal etiology was based on the MRI findings.

We recommend that invasive fungal sinusitis should be kept in mind in suspicious neuro-ophthalmic cases even in mild cases of COVID-19 infection especially in diabetic patients who were given systemic steroids. We also strongly recommend physician and patient education so as to create awareness especially in diabetic or immunocompromised patients, who have recovered or are recovering from COVID-19 because certain neuro-ophthalmic manifestations may require urgent intervention to achieve effective management and prompt treatment to reduce the morbidity and mortality.

STATEMENT OF AUTHORSHIP

Category 1: a. Conception and design: V. M. Shah; b. Acquisition of data: V. K. Hema and K. Kumar; c. Analysis and interpretation of data: V. M. Shah, V. K. Hema, and K. Kumar. Category 2: a. Drafting the manuscript: V. K. Hema and K. Kumar; b. Revising it for intellectual content: V. M. Shah. Category 3: a. Final approval of the completed manuscript: V. K. Hema, K. Kumar, and V. M. Shah.

REFERENCES

1. Li X, Zai J, Zhao Q, Nie Q, Li Y, Foley B, Chaillon A. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARA-CoV-2. *J Med Virol*. 2020;92:602–611.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506.
3. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *J Med Virol*. 2020;92:441–447.
4. Ortez-Seller A, Martínez Costa L, Hernández-Pons A, Valls Pascual E, Solves Alemany A, Albert-Fort M. Ophthalmic and neuro-ophthalmic manifestations of coronavirus disease 2019. *Ocul Immunol Inflamm*. 2020;28:1285–1289.
5. Luís ME, Hipólito-Fernandes D, Mota C, Maleita D, Xavier C, Maio T, Cunha JP, Tavares Ferreira J. A Review of neuro-ophthalmological manifestations of human coronavirus infection. *Eye Brain*. 2020;12:129–137.
6. Das S, Rastogi A, Harikumar KVS, Dutta D, Sahay R, Kalra S, Ghosh S, Gupta SK, Pandit K, Jabbar PK, Damodaran S, Nagesh VS, Sheikh S, Madhu SV, Bantwal G. Diagnosis and management considerations in steroid-related hyperglycemia in COVID-19: a position statement from the endocrine society of India. *Indian J Endocrinol Metab*. 2021;25:4–11.
7. Solanki B, Chouhan M, Shakrawal N. Mucor alert: triad of COVID-19, corticosteroids therapy and uncontrolled glycemic index. *Indian J Otolaryngol Head Neck Surg*. 2021;1–3. doi:10.1007/s12070-021-02801-8.
8. Chwalisz BK, Dinkin MJ. Disease of the year: COVID-19 and its neuro-ophthalmic complications. *J Neuroophthalmol*. 2020;40:283–284.
9. Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, Sharma M, Sachdev M, Grover AK, Surve A, Budharapu A, Ramadhin AK, Tripathi AK, Gupta A, Bhargava A, Sahu A, Khairnar A, Kochar A, Madhavani A, Shrivastava AK, Desai AK, Paul A, Ayyar A, Bhatnagar A, Singhal A, Nikose AS, Bhargava A, Tenagi AL, Kamble A, Nariani A, Patel B, Kashyap B, Dhawan B, Vohra B, Mandke C, Thrishulamurthy C, Sambare C, Sarkar D, Mankad DS, Maheshwari D, Lalwani D, Kanani D, Patel D, Manjandavida FP, Godhani F, Agarwal GA, Ravulaparthi G, Shilpa GV, Deshpande G, Thakkar H, Shah H, Ojha HR, Jani H, Gontia J, Mishrikotkar JP, Likhari K, Prajapati K, Porwal K, Koka K, Dharawat KS, Ramamurthy LB, Bhattacharyya M, Saini M, Christy MC, Das M, Hada M, Panchal M, Pandharpurkar M, Ali MO, Porwal M, Gangashetappa N, Mehrotra N, Bijlani N, Gajendragadkar N, Nagarkar NM, Modi P, Rewri P, Sao P, Patil PS, Giri P, Kapadia P, Yadav P, Bhagat P, Parekh R, Dyaberi R, Chauhan RS, Kaur R, Duvesh RK, Murthy R, Dandu RV, Kathiara R, Beri R, Pandit R, Rani RH, Gupta R, Pherwani R, Sapkal R, Mehta R, Tadepalli S, Fatima S, Karmarkar S, Patil SS, Shah S, Shah S, Shah S, Dubey S, Gandhi S, Kanakpur S, Mohan S, Bhomaj S, Kerkar S, Jariwala S, Sahu S, Tara S, Maru SK, Jhavar S, Sharma S, Gupta S, Kumari S, Das S, Menon S, Burkule S, Nisar SP, Kaliaperumal S, Rao S, Pakrasi S, Rathod S, Biradar SG, Kumar S, Dutt S, Bansal S, Ravani SA, Lohiya S, Ali Rizvi SW, Gokhale T, Lahane TP, Vukkadala T, Grover T, Bhesaniya T, Chawla U, Singh U, Une VL, Nandedkar V, Subramaniam V, Eswaran V, Chaudhry VN, Rangarajan V, Dehane V, Sahasrabudhe VM, Sowjanya Y, Tupkary Y, Phadke Y. Members of the collaborative OPAHJO study on mucormycosis in COVID-19 (COSMIC) study group. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - collaborative OPAHJO study on mucormycosis in COVID-19 (COSMIC), report 1. *Indian J Ophthalmol*. 2021;69:1670–1692.
10. Tisdale AK, Chwalisz BK. Neuro-ophthalmic manifestations of coronavirus disease 19. *Curr Opin Ophthalmol*. 2020;31:489–494.
11. Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. *J Neurol Sci*. 2020;419:117179.