Invasive Fungal Sinusitis in COVID-19 patients seen in South India

Running title: COVID-19 in India

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Key Words: COVID-19; cranial nerve palsy; India; fungal sinusitis, steroids
Abstract:

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 diabetics 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 done, including their co-morbidities, symptoms, cranial nerves involved, ocular and neuroimaging findings, site of lesion, etiology and prognosis.

Results

Most of the patients (7/10), presented with multiple cranial nerve palsies (MCNP) with poor visual acuity. 2/10 cases succumbed to death due to the intracranial involvement. All MCNP had uncontrolled diabetes with 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 diabetics 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.
On March 11, 2020 the World Health Organisation 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 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 like 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, following inadvertent use of systemic steroids in the management of COVID-19 disease (6).

The objective our study was to analyse a series of ten reverse transcription polymerase chain reaction (RT-PCR) positive COVID-19 patients 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 majority of 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, seven from September to November 2020 (first COVID wave) and three in May 2021 (second COVID
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 negative were excluded from this study. For all the patients detailed history, refraction, slit lamp, neuro-ophthalmologic & fundus examination were done. Neuroimaging was done for all. Data was collected from our electronic medical records and retrospectively evaluated for these patients. Informed consent was taken from all the patients and the study was approved by the Institutional Review Board.

Results

Our case series had 7 patients that 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. Out of our case series of 10 patients, 7 were between 45 and 55 years old, others were 69 years, 71 years and 33 years old. 80% (8/10) of our cases were males. Three cases presented with diplopia and had isolated nerve palsy; two with 6th nerve and one with superior division of 3rd nerve palsy. The remaining 7 patients had multiple cranial nerve palsies and in whom drooping of eyelid and pain was the main presenting complaint. All the 3 isolated nerve palsies had no systemic illnesses and normal vision. But in multiple cranial nerve palsies patients, all had uncontrolled diabetes, and 5 had 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 prior to 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 positive following or simultaneously with neuroophthalmological presentation and gave no history of prior diagnosis.

Magnetic resonance imaging of 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 biopsy report). 2 patients had normal neuroimaging. Reports of two patients with chest imaging were available, which were normal. Patients with mononeuropathy had good prognosis. 5 multiple cranial nerve palsy patients who had undergone neurologist and ear, nose and throat specialists (ENT) 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 out of 10 patients), it can also indirectly cause multiple cranial nerve palsies (7 out of 10 patients) secondary to invasive fungal sinusitis because of 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 six cases were given systemic steroids. The cause of sinusitis can be attributed to administration of steroids in diabetics leading to increase in blood sugars which leads to an immunocompromised state causing opportunistic infections like muromycosis 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 COVID-19 patients in India (7) and has also been reported in various parts of the world (8). This is probably related to the steroid usage during 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 corona virus 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. Since the central and peripheral nervous system can be affected, neuro -ophthalmic manifestations can occur (5).

Several case reports and articles document neuro-ophthalmic manifestations of COVID-19 (increased incidence of papilledema, ophthalmpoplegia, isolated cranial nerve palsies, optic neuritis to name a few). However, in our case series of 10 patients, we attempt to analyse 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 palsy on presentation had poor vision and also had poor visual prognosis. Unfortunately, due to late presentation, and intracranial spread, lead to the mortality in 2 patients. Multiple cranial nerve palsies were seen in patients with comorbidities; uncontrolled diabetes secondary to systemic steroid administration being a major precursor in our study.
New treatment protocols have been put into place to combat this new crisis in India, in order to reduce the mortality. As these cases present quite late to us, physicians should be cautioned in administering steroids in diabetics 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 COVID-19 patients 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 COVID-19 patients varies from hospital to hospital. Most of our patients had not done chest computed tomography (CT) imaging as 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 diabetics 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 as certain neuro ophthalmic manifestations may require urgent intervention, in order to achieve effective management and prompt treatment to reduce the morbidity and mortality.
References


Statement of Authorship

Category 1:

a) Conception and design
Virna M. Shah

b) Acquisition of data
V.K. Hema and Karthik Kumar

c) Analysis and interpretation of data
Virna M. Shah, V.K. Hema and Karthik Kumar

Category 2:

a) Drafting the manuscript
V.K. Hema and Karthik Kumar

b) Revising it for intellectual content
Virna M. Shah

Category 3:

a) Final approval of the completed manuscript
V.K. Hema, Karthik Kumar and Virna M. Shah
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age / Gender</th>
<th>Eye</th>
<th>Presenting symptoms</th>
<th>Duration</th>
<th>BCVA &amp; CN</th>
<th>Covid treatment details</th>
<th>Co morbidity</th>
<th>MRI findings</th>
<th>Etiology on MRI</th>
<th>Final outcome</th>
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<td>49 / M</td>
<td>OD</td>
<td>Diplopia</td>
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<td>20/20 VI</td>
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<td>Full recovery</td>
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<td>2</td>
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<td>2 months</td>
<td>20/40 III &amp; VI</td>
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<td>DM</td>
<td>Acute invasive fungal sinusitis</td>
<td>Fungal</td>
<td>ENT &amp; Neurologist referral</td>
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<td>Lid drooping</td>
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<td>7 days</td>
<td>No PL I to VI</td>
<td>Hospital admission (PH/Cef)</td>
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<td>Cerebritis, CST, invasive fungal sinusitis</td>
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<td></td>
<td>Vision loss</td>
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<td>OS</td>
<td>Vision loss</td>
<td>20 days</td>
<td>PL + II, III, VI</td>
<td>No steroids</td>
<td>DM &amp; HT</td>
<td>Inflammatory soft tissue thickening at orbital apex</td>
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<td>Treated with IVMP &amp; oral steroids. Recovered with visual deficit</td>
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<td>Complete recovery</td>
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<td>No PL I to VI</td>
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<td>DM</td>
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<td>2 weeks</td>
<td>HM II, III</td>
<td>Hospital admission with steroids</td>
<td>DM</td>
<td>Acute infarcts in left frontal &amp; parietal lobes Soft tissue thickening at level of orbital apex, superior orbital fissure &amp; cavernous sinus with</td>
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<td>Referral</td>
<td>Outcome</td>
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<td>8</td>
<td>53</td>
<td>M</td>
<td>OS</td>
<td>Lid drooping, Pain &amp; swelling</td>
<td>3 weeks</td>
<td>II to VI</td>
<td>Hospital admission with Doxy, Ivermectin, Remdisivir, Dexa</td>
<td>DM</td>
<td>Invasive fungal sinusitis, left perineuritis with preseptal cellulitis, Intracranial abscess, pachy meningitis, SOV thrombosis</td>
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<td>M</td>
<td>OS</td>
<td>Lid drooping, Fever</td>
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<td>20/200 II to V</td>
<td>Hospital admission with AZ, Ivermectin, Doxy, Dexa</td>
<td>DM</td>
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<td>20/20 III</td>
<td>Home quarantine</td>
<td>Nil</td>
<td>Normal</td>
<td>Inflammatory Complete recovery</td>
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