

Original research article

Cranial nerve involvement in Covid- 19: A prospective study

1. DR.S. BAKYARAJ, 2.DR.G.SIVAGAMI*, 3.DR.M.RAVEENDRAN

4. DR.R.PRASHANTHI, 5.DR.T.RAVIKUMAR

1. ASSISTANT PROFESSOR OF MEDICINE, GOVERNMENT MEDICAL COLLEGE AND ESI HOSPITAL, COIMBATORE

2. ASSISTANT PROFESOR OF PHYSIOLOGY, KARPAGAM FACULTY OF MEDICAL SCIENCE AND RESEARCH, COIMBATORE

3. DEAN& PROFESSOR OF MEDICINE, GOVERNMENT MEDICAL COLLEGE AND ESI HOSPITAL, COIMBATORE

4. INTERNEE, K.G. HOSPITAL AND POSTGRADUATE MEDICAL INSTITUTION,COIMBATORE

5. MEDICAL SUPERINTENDENT&PROFESSOR OF MEDICINE ,GOVERNMENT MEDICAL COLLEGE AND ESI HOSPITAL, COIMBATORE

CORRESPONDING AUTHOR*

ABSTRACT:

BACKGROUND : Involvement of cranial nerves in Covid-19 is not un common, but usually few (smell and taste)and mild ,but in patients with severe COVID-19, especially requiring mechanical ventilation, , and in particular GBS, involvement of multiple cranial nerves should not be missed.

AIM OF STUDY: To study the patho physiology, presentation, outcome of cranean nerve dysfunctions in covid 19 patients .

MATERIALS AND METHODS : All the patients Admitted with RTPCR positive covid -19 are taken for study in Government Medical Medical College and ESI Hospital in Coimbatore, Tamilnadu, India from March2019 to November 2021.

RESULTS AND CONCLUSION : Total number of covid-19 positive patients admitted and treated are 29,170 of them 9421 are diabetic , involvement of first and seventh cranial nerve are 89%(25,961) and 76%(22,169) resulting in anosmia and loss of taste, .001%(29) had involvement of sixth cranial nerve resulting in abduction palsy, involvement of glossopharyngeal and vagus results in 26%(7,584)percent of patients with vagus nerve problems faced long-term issues with their voice, a hard time swallowing, reflux,dizziness, a high heart rate, low blood pressure, and diarrhea. 96 % reverted to normal in 4weeks .

KEYWORDS: SARS-CoV-2, Anosmia, COVID-19, Cranial nerves disorders

INTRODUCTION

On physiological smell, odoriferous substances bind to proteins secreted by sustentacular cells in order to be processed by olfactory receptor neurons.. the main mechanism is Associated with olfactory epithelium damage, targeting predominantly non-neuronal cells. However, neuronal cells can also be affected, worsening the condition of olfactory loss. Whether anosmia/hyposmia and ageusia/hypogeusia are truly attributable to the involvement of cranial nerves I, VII, IX, and X, respectively, in each case is unknown, since only a small portion of these patients undergoes investigations of cranial nerve involvement and since it is conceivable that ageusia or anosmia results rather from the affection of appropriate receptors in mucous membranes than of the nerve. However, if the virus goes intercellularly, it is quite likely that the cranial nerves most frequently involved in COVID-19 are cranial nerves I, VII, IX, and X, as the prevalence of hyposmia/anosmia and hypogeusia/ageusia is high in several studies. Anyhow, as long as anosmia and hypogeusia are not confirmed by MRI or other means, they may not be classified

as involvement of appropriate cranial nerves. Involvement of FIRST cranial nerve should be diagnosed only if imaging demonstrates affection of the olfactory bulb or the fila olfactoria or if autopsy demonstrates the virus within olfactory neurons. If retrograde migration of the virus along olfactory or gustatory pathways can be confirmed, the frequency of cranial nerves I, VII, IX, and X needs to be re-assessed.

AIM OF STUDY:

To study the patho physiology, presentation, outcome of cranial nerve dysfunctions in covid 19 patients .

MATERIALS AND METHODS:

All the patients Admitted with RTPCR positive covid -19 are taken for study in Government Medical College and ESI Hospital in Coimbatore, Tamilnadu, India from March 2019 to November 2021.

RESULTS:

Total number of covid-19 positive patients admitted and treated are 29,170 of them 9421 are diabetic , involvement of first and seventh cranial nerve are 89%(25,961) and 76%(22,169) resulting in anosmia and loss of taste, .001%(29) had involvement of sixth cranial nerve resulting in abduction palsy, involvement of glossopharyngeal and vagus results in 26%(7,584)percent of patients with vagus nerve problems faced long-term issues with their voice, a hard time swallowing, reflux,dizziness, a high heart rate, low blood pressure, and diarrhea. 96 % reverted to normal in 4weeks .

DISCUSSION:

A second hypothesis explaining cranial nerve involvement relies on the assumption that immunological reactions against the virus secondarily affect neuronal structures due to epitope mimicry as in GBS. Arguments in favor of the radiculitis hypothesis are that cranial nerve involvement frequently occurs in patients with GBS and that patients with GBS and cranial nerve involvement may present with DCA or positive OCB on CSF investigations. An argument against the radiculitis hypothesis, however, is that imaging studies hardly revealed impairment of proximal portions of cranial nerves clinically involved in COVID-19. Interestingly, patients have been reported in whom MRI revealed enhancement of cranial nerves without corresponding clinical abnormalities .Absence of cranial nerve II involvement in GBS patients could be explained by classification of the optic nerve as part of the CNS and not as cranial nerve. Whether involvement of the optic nerve in COVID-19 favors the development of demyelinating disease remains elusive but several cases with SARS-CoV-2 associated optic neuritis have been reported since the end of January 2021. Long-term evaluation of these patients is crucial to assess if SARS-CoV-2 triggers multiple sclerosis or neuromyelitis optica. As soon as a cranial nerve lesion becomes evident on a clinical exam in a patient with COVID-19 cerebral imaging is mandatory.

A third hypothesis explaining the involvement of cranial nerves in COVID-19 relies on the assumption that drugs given to treat COVID-19 could exhibit neurotoxic side effects particularly damaging cranial nerves. Drugs known to cause neuropathy and frequently given to COVID-19 patients include daptomycin ,linezolid ,lopinavir ,ritonavir ,hydro-chloroquine ,cisatracurium ,clindamycin ,tocilizumab, and glucocorticoids

Treatment of cranial nerve involvement relies on the application of anti-COVID-19 drugs and more specifically on the application of steroids, particularly in patients with isolated cranial nerve involvement, of IVIG,

In patients with severe COVID-19 under mechanical ventilation, transcutaneous, non-invasive vagal nerve stimulation has been shown to improve lung functions

CSF investigations are usually normal in COVID-19 patients with isolated involvement of cranial nerves but show dissociation cyto-albuminiquie (DCA) or positive oligoclonal bands (OCB) in patients with GBS and concomitant cranial nerve involvement

PATHO PHYSIOLOGY

Both human cell receptors ACE2 and TMPRSS2 are essential for the SARS-CoV-2 entrance. These receptors are mostly present in the olfactory epithelium cells, therefore, the main hypothesis is that anosmia is caused due to damage to non-neuronal cells which, thereafter, affects the normal olfactory metabolism. Furthermore, magnetic resonance imaging studies exhibit a relationship between a reduction on the neuronal epithelium and the olfactory bulb atrophy. Damage to non-neuronal cells explains the average recovery lasting a few weeks. This injury can be exacerbated by an aggressive immune response, which leads to damage to neuronal cells and stem cells inducing a persistent anosmia. Conductive anosmia is not sufficient to explain most cases of COVID-19 induced anosmia.

SARS-CoV-2 CTD also has more van der Waals bonds, hence it binds with greater affinity to ACE2. Some tissues express ACE2, such as lungs, heart, oral and nasal mucosa rinses, testicles, intestines, lymphoid organs and brain, as a result, they are more susceptible to the invasion of –virus Nevertheless, the main entry route inside the organism is through the nasal mucosa

In addition, a study demonstrated a possible correlation between anosmia and IL-6 levels. IL-6 induces the expression of several acute-phase proteins, among them C-reactive protein, serum amyloid A, α 1-antiquimotripsin, haptoglobin, fibrinogen and complement components. Therefore, patients with higher levels of IL-6 may be associated with more intense cases of olfactory disorders. The high production of cytokines can provoke olfactory neurons death. The olfactory epithelial neurons replacement by basal stem cells requires a longer recovery time, thus explaining persistent anosmia cases.

Loss of smell may be due to olfactory bulb inflammation triggered by virus infection. SARS-CoV has the ability to infect the central nervous system through the synapses, using the olfactory nerve afferents to reach the olfactory bulb, raising the possibility of SARS-CoV-2 utilizing this infection path as well.

Epidemiological factors such as age and lifestyle directly interfere with the prevalence of olfactory disorders.

Gutiérrez-Ortiz describe one patient with Miller Fisher syndrome (MFS) and another with cranial neuropathies. Both developed ocular motility deficits after a viral prodrome of fever, anosmia, and ageusia. The patient with MFS had elevated CSF protein, positive serum anti-GD1b ganglioside antibodies, and a swift therapeutic response to IV immunoglobulin (IVIg). Both patients had lymphopenia, yet their CSF was acellular and aseptic.

Dinkin et al. describe 2 patients with COVID-19 with ocular motor palsies and mild respiratory symptoms. One, with presumed MFS, had MRI features of oculomotor nerve thickening and enhancement. A second, presenting with an isolated sixth nerve palsy, demonstrated MRI enhancement of the optic nerve sheaths and posterior Tenon capsules. These features were interpreted as viral leptomeningeal invasion, despite normal CSF. Both reports illustrate early occurrence of cranial neuropathies in COVID-19, and highlight the importance of recognizing this

clinical association, particularly in patients with hypogeusia, hyposmia, and lymphopenia. The strength of the report by Gutiérrez-Ortiz et al. is the demonstration of MFS with GD1b antibodies, whereas Dinkin et al. present novel imaging findings. Together, they inform our growing understanding of COVID-19–associated Guillain-Barré syndromes (GBS), which often affect cranial nerves

The association between cranial neuropathies and COVID-19 provides the impetus to explore neuroinvasion and autoimmunity. Evidence of neurologic injury has been described in patients infected with SARS-CoV and MERS-CoV, potentially arising from hematogenous spread or neuronal retrograde dissemination. Specifically, COVID-19 may infect endothelial cells, compromising the integrity of the blood–brain barrier, or infiltrate leukocytes that become subsequent viral reservoirs for dissemination. Macrophages expressing ACE2 receptors may augment systemic inflammation, perpetuating widespread tissue injury. Coronaviruses may also access the nervous system through neuroepithelium of the olfactory nerve and olfactory bulb or via retrograde axonal transport through other cranial nerves. Indeed, cranial nerve involvement may reflect COVID-19 neurovirulence, because anosmia affects up to 50% of infected patients. Interestingly, MRI features depicting cranial nerve, root, and meningeal involvement may represent neuroinvasion, or alternatively edematous neuroinflammation.

There is mounting evidence that cranial nerve involvement in COVID-19 represents autoimmunity, as in GBS cases. First, GBS is the prototypical postviral induced neuropathy seen in 70% of cases with known triggers, including influenza, enteroviruses, H1N1, West Nile virus, Zika, MERS-CoV, and SARS-CoV.⁷ Second, in 7 of 11 tested patients with COVID-19 GBS, the virus was absent in acellular CSF, implying no direct root infection or intrathecal viral replication. Third, the noted improvement with IVIg suggests an ongoing immune response, similar to other autoimmune disorders. Fourth, the anti-GD1b ganglioside antibodies in the patient with MFS, contrary to typically observed anti-GQ1b, suggest novel implications. Gangliosides, particularly those containing a disialosyl moiety (GD1b, GQ1b, and GT1b), serve as antigens in patients with neuropathies. When immunoglobulins recognize epitopes containing disialosyl groups of GD1b on dorsal roots, a sensory ataxic neuropathy can result, including ophthalmoplegia.

The role of gangliosides in driving peripheral nerve autoimmunity is intriguing, because attachment of COVID-19 spike S-proteins to respiratory cells is mediated not only by ACE2 receptors, but also by binding to sialic acid–containing glycoproteins and gangliosides on cell surfaces. Accordingly, cross-reactivity between epitopes within the COVID-19 spike-bearing gangliosides and signature sugar residues of surface peripheral nerve glycolipids is a possibility. Such molecular mimicry exists between peripheral nerve glycolipids and *Campylobacter jejuni* and Zika virus infections, which are known triggers for GBS. Considering that gangliosides within ocular motor nerves account for antiganglioside antibodies seen in some postinfectious ophthalmoplegias, such cross-reactivity may explain cranial neuropathies in COVID-19. Finally, the binding affinity of chloroquine to sialic acids and gangliosides has notable treatment implications. In the presence of chloroquine, the SARS-CoV viral spike cannot bind gangliosides to infect targeted cells. Whereas clinical improvement was observed in one treated patient with COVID-19 MFS, the therapeutic role of chloroquine remains unclear.

The global pandemic has underscored the need to understand the neurotropic potential of COVID-19 and mechanisms by which the virus may trigger autoimmunity. To this end, neurologists have a vital role to play.

Vigilance will be needed to detect and treat COVID-19–related immune-mediated disorders. To the extent possible, screening for autoantibodies in cases of neuropathies, myopathies, and encephalitides should be performed. Moreover, early initiation of immunotherapy, specifically IVIg, should be considered, when indicated clinically, to offer protective antibodies, ameliorate cytokine effects, and facilitate hospital discharge.

Involvement of a cranial nerve results from the uptake of the virus into the intracellular space of neurons at a distal location followed by retrograde transport of the virus particles to the brain. An argument for this hypothesis is that in an autopsy study of 43 patients deceased from COVID-19 SARS-CoV-2 viral proteins were detected in cranial nerves originating from the lower brainstem and in isolated brainstem cells

Furthermore, virus particles have been repeatedly found in neurons but also axons of cranial nerves in other autopsy studies .Experimental studies indicate that SARS-CoV-2 indeed migrates retro-gradually within axons of cranial nerves to the CNS

majority of cases with isolated cranial nerve involvement benefit from steroids, whereas GBS cases with cranial nerve involvement benefit from IVIG. The outcome in isolated cases is usually fair with more patients reaching complete recovery than partial recovery. On the contrary, GBS patients with cranial nerve involvement more frequently achieve partial recovery as compared to complete recovery.

There are many studies showing that COVID-19 infection is neurotropic and neuroinvasive The most common neurological symptoms in COVID-19 are encephalopathy, acute cerebrovascular diseases, and acute polyradiculopathy or neuropathies .Neurological symptoms may occur as direct effects of SARS-CoV-2 virus neurotropism on central and peripheral nervous systems (CNS and PNS), or as a systemic consequence of a para-infectious or post-infectious immune-mediated mechanism .It is considered that the virus reaches CNS via neuronal retrograde transmission or hematological spread. In addition, the effects on CNS and PNS are thought to occur through the virus entering the cell using ACE-2 receptors However, it is not known whether cranial nerve involvement is directly caused by CNS or the direct invasion of peripheral nerves nor is it clear whether this damage is caused directly by the virus or the immune system response triggered by the virus. There are many publications reporting that the cranial nerves are affected by COVID-19. Mao et al. evaluated neurological symptoms in 214 patients infected with COVID-19. It was observed that 36.4% of these 214 patients who were hospitalized had nervous system findings such as dizziness, headache, taste disturbance, hyposmia, muscle damage, and hemorrhagic and ischemic brain damage .However, Mao et al. observed the effects of the virus on peripheral nerves and CNS rather than cranial nerves. We consider that the emergence of neurological findings alone is not an indicator of poor prognosis, as previously assumed because we did not determine a statistically significant difference between the groups with and without cranial nerve involvement in terms of length of hospital stay and intensive care requirement. In particular, both in our study and among the reported cases, the presence of patients with complaints such as sudden vision loss, sudden hearing loss, sudden-onset severe peripheral vertigo, and sudden movement limitation in the eye suggests that COVID-19 involves aggressive neurotropism and neuroinvasion. The current literature contains reports on cranial nerve involvement in patients with COVID-19; e.g., dysphagia caused by N. glossopharyngeus, N. vagus and N. hypoglossus damage ,as well as presence of damage to N. vestibulocochlearis ,N. facialis ,N. oculomotorius ,N. abducens ,N. trochlearis N. opticus and N. olfactorius .COVID-19 has also been

reported to cause neurological syndromes such as Guillain–Barré syndrome and Miller Fisher syndrome. Despite all these data, we did not find any study on the prevalence of these cranial nerve symptoms in patients in the current literature. In a study conducted by Mao et al., damage to the peripheral nervous system and CNS was discussed in the majority of patients, but cranial nerve functions were not emphasized, except for taste and smell disorders. Bagheri et al. investigated olfactory disorders in people infected with COVID-19, but only used an online survey to identify patients. In the current study, we tried to evaluate all cranial nerve involvements together in people infected with COVID-19 and to reveal their prevalence in infected patients. For this purpose, we deemed it appropriate to make a diagnosis based on a direct examination. Only after the patients' discharge from the hospital, we administered the survey through phone calls to determine the development or regression of existing symptoms. However, we can state that there are still some important points that have not yet been fully explained. Although we still cannot explain the exact mechanism, some cranial nerves are affected more frequently in the very early period while others occur later. For example, while patients had symptoms of a very high degree of loss of taste and smell at the time of direct presentation, they rarely presented with ophthalmoparesis, dysphagia, or vision and hearing loss. In a multicentric survey study conducted in 12 hospitals from different regions of Europe, the rate of loss of smell and taste in COVID-19-infected patients was found to be 85.6% and 88.0%, respectively. This led us to consider that the most important factors for this virus settled in the respiratory tract to cause cranial nerve damage are the response it triggers in local immunity and direct nerve invasion. As we mentioned earlier, if the most common symptoms of loss of smell (27.2%) and taste (30.8%) had occurred as a result of damage caused by the virus in CNS or systemic immune response, we would expect it to occur at a frequency close to other cranial nerve involvement. However, while *N. facialis* and *N. ophthalmicus*, the cranial nerves that are closest to the respiratory tract and branch into this region, are frequently affected, *N. hypoglossus*, *N. glossopharyngeus*, *N. vagus*, and *N. trigeminus* were less frequently involved, which raises further questions that need to be answered. Nevertheless, we believe that the size of the areas in which these nerves innervate in the respiratory tract will naturally increase their exposure, which is a factor to be considered in explaining this situation. Another important finding of our study was that among the patients hospitalized due to COVID-19, those with swallowing disorders due to glossopharyngeal and vagal nerve involvement had a more severe disease process and required a longer hospital stay since their food intake was impaired.

CONCLUSION

In patients with cranial nerve involvement COVID-19 infections are usually mild. Isolated cranial nerve palsy without GBS usually responds favorably to steroids. GBS with cranial nerve involvement benefits from IVIG. COVID-19 disease caused by the SARS-CoV2 virus commonly leads to cranial nerve symptoms. During our study, we observed symptoms of the involvement of very different cranial nerves apart from taste and smell disorders reported. However, further studies are needed to provide more definitive results concerning whether these nerve damages are permanent or temporary. Our first impression is that symptoms such as smell, taste, vision and sudden hearing loss, vertigo, swallowing disorders, hoarseness, eye symptoms, and facial hypoesthesia completely disappear within the first month of the infection. Taste and smell disorders rarely last more than one month. Therefore, we consider that these symptoms often do not require any special treatment, and cranial nerve symptoms

regress with the current COVID-19 treatment protocol. In addition, as an interesting finding, we determined the dominant effect of cranial nerve involvement on sensory dysfunction compared to motor functions.

References:

1. Selvaraj V., Sacchetti D., Finn A., Dapaah-Afriyie K. Acute vision loss in a patient with COVID-19. *R I Med J (2013)* 2020;103(6):37–38.
2. Mao L., Jin H., Wang M., Hu Y., Chen S., He Q. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683–690.
3. Yachou Y., El Idrissi A., Belapasov V., Ait Benali S. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. *Neurol Sci.* 2020;41(10):2657–2669.
4. Yavarpour-Bali H., Ghasemi-Kasman M. Update on neurological manifestations of COVID-19. *Life Sci.* 2020;257
5. Poyiadji N., Shahin G., Noujaim D., Stone M., Patel S., Griffith B. COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *J Radiology.* 2020;201187
6. Cavalagli A., Peiti G., Conti C., Penati R., Vavassori F., Taveggia G. Cranial nerves impairment in post-acute oropharyngeal dysphagia after COVID-19: a case report. *Eur J Phys Rehabil Med.* 2020 Dec;56(6):853–857. doi: 10.23736/S1973-9087.20.06452-7.
7. Chen X., Laurent S., Onur O.A., Kleineberg N.N., Fink G.R., Schweitzer F. A systematic review of neurological symptoms and complications of COVID-19. *J Neurol.* 2020:1–11.
8. Lima M.A., Silva M.T.T., Soares C.N., Coutinho R., Oliveira H.S., Afonso L. Peripheral facial nerve palsy associated with COVID-19. *J Neurovirol.* 2020;26(6):941–944
9. Dinkin M., Gao V., Kahan J., Bobker S., Simonetto M., Wechsler P. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology.* 2020;95(5):221–223.
10. Falcone M.M., Rong A.J., Salazar H., Redick D.W., Falcone S., Cavuoto K.M. Acute abducens nerve palsy in a patient with the novel coronavirus disease (COVID-19) *J AAPOS.* 2020;24(4):216–217.
11. Oliveira R.M.C., Santos D.H., Olivetti B.C., Takahashi J.T. Bilateral trochlear nerve palsy due to cerebral vasculitis related to COVID-19 infection. *Arq Neuropsiquiatr.* 2020;78(6):385–386.
12. Selvaraj V., Sacchetti D., Finn A., Dapaah-Afriyie K. Acute vision loss in a patient with COVID-19. *R I Med J (2013)* 2020;103(6):37–38.