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Intranasal Route: A Nasocerebral Approach against SARS-CoV-2 in NeuroCOVID

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ABSTRACT: The nasal cavity is a prime site for viral load of SARS-CoV-2 in COVID-19, as is evident from the fact that this area has been used for sample collection for the diagnosis of COVID-19. The nasal cavity has a connection with the brain across the cribriform plate which has been reported to be a route of SARS-CoV-2 to the olfactory apparatus and the brain. Targeting the SARS-CoV-2 in the nasal cavity in patients presenting with COVID-19 and long-COVID can result in the prevention and treatment of neurological deficits and therefore needs to be prioritized as a route of potential significance.

KEYWORDS: *NeuroCOVID, viral loads, COVID-19 vaccines, COVID-19 treatment, transcribrial route*

A. INTRODUCTION

SARS-CoV-2 uses the oral and the nasal cavities as its prime routes of infection. These sites of entry enable it to reach the lungs where it evokes the majority of symptoms following damage to the lung tissue resulting in hypoxia. Very early in the course of the disease, the infection in COVID-19 spreads to diverse organs and tissues resulting in a systemic illness. Of the systems and organs involved, the central nervous system (CNS) is the most sensitive and vulnerable organ due to its limited ability to tackle hypoxia, injury inflicted by an inflammatory reaction, and injury caused by direct neuronal damages as has been reported during the pandemic. Contrary to the popular theory of entry into the CNS by causing damage to the blood−brain barrier following a systemic infection, it has been reported that the virus uses the cribriform plate at the roof of the nasal cavity to access the brain and olfactory apparatus enclosed within the cranial cavity. The possibility of transcribrial access to the brain with the SARS-CoV-2 was hinted at for the very first time early during the pandemic,[1] but irrefutable evidence with SARS-CoV-2 mRNA isolated from the olfactory bulb and frontal lobe of the brain that overlay the cribriform plate emerged later.[2] Keeping in mind the proximity of the brain and access to the BBB close to the cribriform plate,[1,2] it can be deduced that the virus can cause an early onset of neuroinflammation and get dispersed to other areas of the CNS like the brainstem, from where it has been isolated in autopsies done in COVID-19 on patients who died of SARS-CoV-2.[2] It is now established that patients with a protracted form of SARS-Cov-2, called long-COVID, continue to exhibit neurological symptoms that, if coexisting with the evidence of biomarkers of SARS-CoV-2 replication, could hint indicate the nasal cavity and the areas of its extension, like the intestines, can serve as potential sites viral hideouts in long-COVID. The viral replication in areas of hideouts could provide an explanation of the continued symptoms of long-COVID and the benefits associated with the use of the intranasal route shows promise as a pathway to administer drugs, vaccines, and neurotropic anti-inflammatory agents. One interesting fact is that the nasal cavity extends to cavities in air sinuses like (a) maxillary, ethmoid, frontal and (b) to the middle ear, and (c) cranial cavity provides the virus a chance to persist in these places. The paucity of blood flow to these areas (and resulting limited access to antibodies and systemic drugs), along with the mucosal lining with ACE2 and NRP-1 receptor expression, makes them ideal for viral persistence and replication. Killing the SARS-CoV-2 in these potential sites, and pairing this treatment approach with similar areas in the gut, may eradicate the virus and help in the treatment of long-COVID patients. This paper discusses vaccines, drugs, and other treatment modalities of potential that have been and can be used as intranasal medication.

B. USE OF INTRANASAL AND TRANSCRIBRIAL ROUTE IN COVID-19 AND LONG-COVID

The objective of the use of the intranasal route in COVID-19 and long-COVID could be for (a) prophylaxis or (b) treatment of neuroCOVID in these groups of patients. For COVID-19 the trend to use COVID-19 intranasal vaccine has emerged recently and reviewed[3,4] with variable success rates. The use of drugs targeting SARS-CoV-2[5] has been tested in animal models with success. In projecting an animal model study to humans, it would be important to take into consideration the differences in the anatomical structure of the nasal cavity and its extensions to other potential spaces as described above. The differences in the size of the pores in the cribriform plate in

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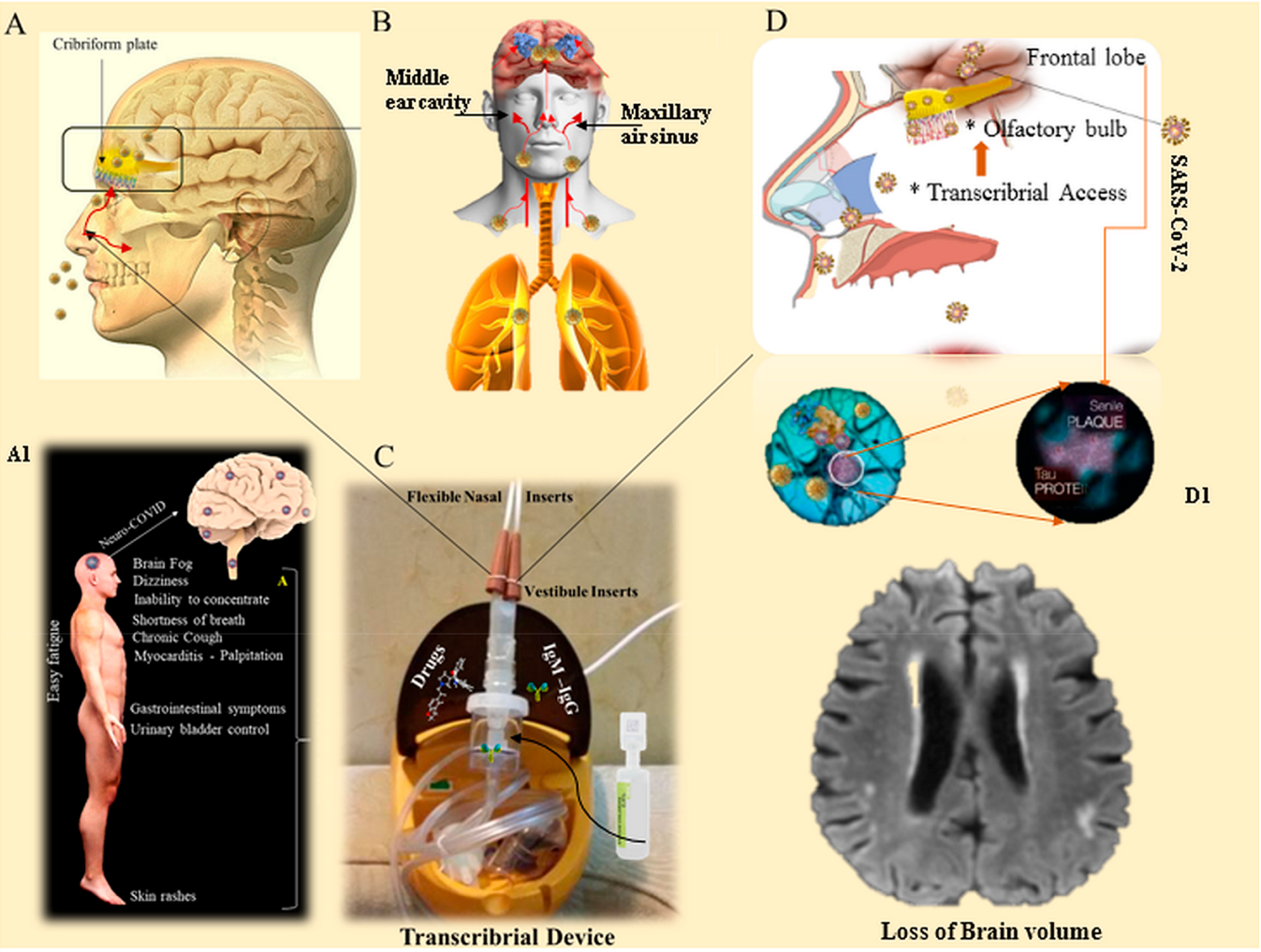

Figure 1. Intra-nasal route (A) is the prime route of SARS-CoV-2 infection in COVID-19. Reports on the use of this route of administration for vaccines and eradication of the residual virus in COVID-19 and long-COVID (A1) have emerged. Sites such as air sinuses (B) can lead to viral persistence and prolonged symptoms. Neubilizers and devices (C) that can deliver drugs, antibodies, and saline can be beneficial in targeting the virus at sites of viral load that has been shown to be trancribrial route to reach the olfactory bulb and adjacent brain lobes (D). The use of a trancribrial device (C) for targeting the SARS-CoV-2 at the root of the nose can prevent early neuro-COVID and future complications including deposition of Spike protein fragments called amyloidogenic peptides to cause neurodegeneration and loss of brain volume (D1) as has been reported in patients recovering from COVID-19.

animals and humans are expected to affect the bioavailability of the fixed dose of vaccines and drugs administered via the intranasal route. The same remains true for the differences in the size of olfactory mucosal zones and sensitivity to the stimuli that evoke action potentials in olfactory pathways.

The rationale for the use of the intranasal route for drugs targeting viral reservoirs in long-COVID and the potential benefits it can offer in these sets of patients needs to be strengthened through further studies. The presence of consistently elevated antibody (IgG) against S-protein and N-protein (nucleocapsid) in the majority of long-COVID patients hints toward viral persistence and an antigenic challenge imposed by the S-protein. In patients with adverse effects events reported after COVID-19 vaccine for prophylaxis, only S-protein IgG has been seen to be elevated in the absence of reinfection. The possible low vascular sites where the virus can conceal and evade the immune response include areas mentioned above and shown below (Figure 1A). Delivery of drugs[5] or saline[6] to these areas by nebulizer or similar devices can enable the SARS-CoV-2 targeting agents to exert antiviral effects topically at these areas where the bioavailability of the drugs or the access of antibodies given via systemic routes would have been lower otherwise. Additional benefits of saline use by nebulizer are that it can act as prophylaxis for newly acquired COVID-19 infection preventing long-COVID in patients in addition to its effect to decrease the viral load[6] and preventing neuroCOVID complications in ongoing long-COVID. The possibility of saline administered via the intranasal route reaching the extension of the nasal cavity in areas including air sinuses, cribriform plate, and the adjacent cavities containing air spaces provides the benefit of exerting a virucidal effect, thereby addressing the viral persistence etiology as a cause of persistent symptoms in long-COIVD.

C. TYPES OF DRUGS AND MOLECULES THAT CAN BE USED INTRANASALLY IN COVID-19 AND LONG-COVID

The prime objective of intranasal therapy in COVID-19 and long-COVID could be the prevention or treatment of the SARS-CoV-2 infection or its effects like neuroinflammation,

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cytokine antagonism, and prevention of cell injury to neuronal and glial cells in olfactory mucosa and cerebral lobes. Symptoms related to neuroCOVID have remained a feature of both acute phase and long-COVID with SARS-CoV-2 infection. When delivery via intranasal route, antibodies directed against the Spike protein of SARS-CoV-2 have been reported to be effective in trials. Also, synthetic drugs and natural products that are safe and efficacious as antiviral, antineuroinflammatory, and antioxidant agents stand a chance to be tested in human clinical trials via the intranasal route to contain the viral replication and inflammatory reaction in neuroCOVID to prevent symptoms such as "brain fog", loss of cognitive functions, anosmia, and amnesia associated with COVID-19 and long-COVID. Molecules like resveratrol, epigallocatechin gallate (EGCG), and melatonin can contain neuroinflammation, and cytokine-mediated neuronal and glial cell damage is being tested in clinical trials to gauge the clinical efficacy and safety of these agents for their use in COVID-19 and long-COVID. Known antioxidants like vitamin E, oleic acid, and ω3 fatty acid molecules added in combination with the above molecules can be considered while manufacturing the formulation for intranasal administration.

D. ADMINISTRATION OF SALINE SOLUTION VIA INTRANASAL ROUTE USING A NEBULIZER OR MODIFIED TRANSCRIBRIAL DEVICES

Saline nasal irrigation in COVID-19 with its effects on viral load, mucosal dynamics, and patient outcomes has been reported and documented recently.[6] Saline irrigation has been reported to be a safe, low-cost, and easy-to-use sanitation measure, complementary to hand washing or mask-wearing. The mechanisms by which saline of various strengths can combat SARS-CoV-2 have been reviewed in detail.[6] The use of a nebulizer can widen the areas covered by the saline inhaled (Figure 1 B) to exert its effect on viral loads in the air sinuses, mouth, throat, and turbines present in the lateral wall of the nose. The mucus liquefication by saline can be an additive benefit of its use. Though the clearance of the viral load from deeper areas like the subcribriform plate zone can be partly achieved by nebulizing, specialized devices reported previously like the "trancribrial apparatus" (Figure 1 C) for drug delivery in infections caused by *Naegleria fowleri* can be tested in clinical trials to show the extent to which this approach can affect the viral loads in COVID-19 and long-COVID. A large well-controlled or surveillance study can help to further validate the outcomes and to implement the use of saline inhalation in COVID-19 and long-COVID.

E. INTRANASAL ROUTE IN MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME (ME/CFS)

The neuroinflammation findings in chronic fatigue syndrome (ME/CFS) and fibromyalgia (FM), while limited to a handful of studies, are still persuasive as to be the leading factor if not the primary cause of these disorders. It is known that several, if not all of the clinical features, and symptoms that are particularly associated with ME/CFS and FM such as cognitive dysfunction, fatigue, pain, and mood fluctuations can have their origins in the CNS. If true, the bigger question remains how to treat the brain in ME/CFS? Getting neuro-anti-inflammatory molecules, antioxidants, and drugs that prevent neurodegeneration in the brain is limited by the BBB. Some studies have found high lactate and low glutathione levels in the ventricles of the brains of ME/CFS patients suggesting: a) high rates of oxidative stress are present in the brains of ME/CFS patients, and b) glutathione is being overwhelmed in the brain of patients with ME/CFS. About ∼20% improvement in 6-8 weeks of fatigue and cognition has been seen within about six to eight weeks, in about 80−90% of some patients treated with intranasal glutathione has been seen in some clinical practice. This highlights the urgency for trials of more soluble antioxidants in patients with ME/CFS to accelerate the recovery from fatigue and improve cognitive function, pain, and dysautonomia. A study done in 2016 confirmed that when taken intranasal, compounded glutathione does indeed increase brain glutathione levels. Although not exclusively considered as a post-infectious entity, ME/CFS has been associated with several infectious agents including Epstein−Barr Virus, Q fever, influenza, and other coronaviruses. There are important similarities between long-COVID /post-acute COVID-19 symptoms and ME/CF. It remains to be established whether as postulated for long-COVID, a viral reservoir exists in ME/CFS or not. In either case, research and urgent clinical trials of drugs such as Resveratrol, Epigallocatechin gallate (EGCG), and Melatonin with other powerful antioxidants like oleic acid, Glutathione, and vitamin E should be funded to find solutions to neglected diseases like ME/CFS.

F. DISCUSSION AND CONCLUSION

At the end of 2019 and the beginning of 2020, the COVID-19 pandemic struck the globe; it continues with so many SARS-CoV-2 mutations that naming them has nearly exhausted the Greek alphabet as epidemiologists seek to identify the emerging variants of this deadly virus, which continues to evade the immune system. The acute COVID-19 emergency caused millions of deaths worldwide and also has been found to cause lingering debilitating symptoms in a state recognized as long-COVID syndrome. The CNS is one of the end organs targeted in both the acute and chronic forms of COVID and has gained recognition as Neuro-COVID in the past 3 years of the pandemic. Initially thought to be an exaggeration of the diverse organ infection capability of SARS-CoV-2, it is now an irrefutable fact that SARS-CoV-2 targets the brain, causing neurological deficits. Moreover, its capability to access the brain via the porous cribriform plate was initially dismissed as a hyperbolic coined to be a hyperbole hypothesis dyed-in-the-wool[1] but was later confirmed to be the disease's pathway to the brain by finding the mRNA all along the olfactory mucosa, olfactory nerves, cribriform plate, olfactory bulb,[2] and inferior surface of the frontal lobe, in that anatomical order from the nasal cavity to the cranial cavity. Recognizing the primacy of this anatomical pathway as a route of infection by COVID, and the resulting neurological deficits that go on to develop in NeuroCOVID, the intranasal route (Figure 1A) appears to be a route of administration of choice for targeting SARS-CoV-2 viral loads (5) in the prevention as well as treatment of neuro-COVID. Non-drug treatment modalities like saline inhalation[6] via nebulizer (Figure 1C) appear to be an effective way of targeting the hideouts of SARS-CoV-2 deep within the air sinuses to minimize the continuing symptoms of long-COVID. It is important to mention here that for other places like the gut, where intestinal lumens and crypts in the glandular cells can serve as a viral reservoir, antiviral drugs and, antibiotics to kill bacteria- harboring SARS-C-Ov-2, and probiotics to restore the intestinal flora would be needed to completely eradicate

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the residual viral loads. Use of topical antibodies and natural products directed against the spike protein of SARS-CoV-2 via the intranasal route offer an additional gain in preventing serious complications following COVID-19 by minimizing hospitalization and the known complications associated with COVID-19 and long-COVID. One forte of the intranasal route to deliver anti-neuroinflammatory drugs and molecules to the nose would be to restore anosmia that has been reported to continue for years after acute COVID-19 infection and is due to persistent inflammation in the olfactory mucosa. Research is needed to fine-tune intranasal devices for more efficient delivery. Funding of clinical trials exploring molecules with the potential to limit inflammation and target the virus in the nose and its extension into adjacent potential spaces is imperative to get success in the treatment of acute and long-term neurological deficits caused by SARS-CoV-2. Research on nasal routes to deliver drugs in long-COVID is expected to prevent the onset of post-infectious ME/CFS in many affected individuals, and will also help in understanding the concept and significance of viral persistence in ME/CFS—a disease for which research has been largely neglected until the onset of the COVID-19 pandemic.

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Notes

The authors declare no competing financial interest.

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