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COVAGAL HYPOTHESIS : THE CONNECTION BETWEEN COVID AND VAGUS .

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ABSTRACT The Coronavirus SARS CoV2 is a part of Coronaviridae family. The virus has overwhelmed the entire world with millions of deaths being reported each day. New variants of the virus are causing havoc in almost all parts of the world. India is witnessing a second wave of this pandemic in 2021. Scrutinizing and correlating data from over thousands of studies, the authors have conceptualized a basic pathophysiology and natural course of the disease. The authors propose a novel understanding of the disease, its epidemiology, symptoms and a targeted treatment protocol for the fatal virus. We shall be referring the SARS CoV2 variant of 2021 causing second wave of pandemic in India as the Rhabid Covid Virus (RCV) for better understanding of our hypothesis. The RCV is a single stranded RNA virus similar to the Rhabdovirus. The Rhabdovirus has neurovirulent action and the human coronaviruses have neuroinvasive properties. The RCV has both neurovirulent and neuroinvasive properties. We have hypothesised that vagus nerve is the main nerve affected by RCV. The symptoms that follow conform to the stages of injury, degeneration and regeneration of vagus nerve along with stages of myelin clearance. Based on our hypothesis, we have classified this disease into three stages. We have also introduced a new treatment protocol contingent on the stage of the disease presented.Our aim behind this hypothesis is to encourage clinical trials based on our protocol such that new and effective targeted treatment can be introduced against this deadly virus.

KEYWORDS : Coronavirus, SARS CoV 2, pandemic, Vagus nerve

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been here for more than 2 years now. The virus was found to be originated in bats.[1] Its transmission in humans is thought to be through a yet unknown intermediate host.[1]

The virus usually spreads by aerosols released by the infected source, although transmission by fomites is also considered probable mode.[2] It attaches to the surfaces of the nasal mucosa/oropharangyeal cavity mucosa/nasopharyngeal mucosa.[2] The patients usually present with fever, sore throat, odynophagia, rhinorrhea, cough, breathlessness, malaise and even diarrhoea.[2] The disease process can result into acute respiratory distress syndrome (ARDS) and even multi organ failure.[2] Tools for diagnosis mainly include viral nucleic acid detection in nasal or oral swabs.[2] As of now, the treatment is mainly supportive and symptomatic. We, hereby, aim to make it more targeted.

The current understanding of covid pathophysiology is that it is an upper respiratory tract infection (URTI) complicated by lower respiratory tract infection (LRTI) leading to lung fibrosis. The mechanism of lung fibrosis is still poorly understood. Involvement of multiple organs and thrombi formation also remains a mystery. Whereas, our hypothesis attempts to explain all the clinical features of this disease with precision.

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The authors propose a novel understanding of the disease, its epidemiology, symptoms and a targeted treatment protocol for the fatal virus. We shall be referring the SARS CoV2 variant of 2021 causing second wave of pandemic in India as the Rhabid Covid Virus (RCV) for better understanding of our hypothesis. The RCV is a single stranded RNA virus similar to the Rhabdovirus.

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THE HYPOTHESIS AND ITS EVALUATION

We hypothesise that after attaching to the mucosal surface of nasopharynx, the RCV is caught by the Waldeyers ring. It is similar to the attachment of EBV virus as in Nasopharyngeal Carcinoma where the EBV attaches to the Fossa of Rossenmuller.[3]

We hypothesise that RCV disease is a viral autoimmune neurological disorder with rapid progression, which mimics rabies, neurotoxic snake-bite, acute stage of myasthenia gravis and nasopharyngeal carcinoma at some stage of its progression. According to our hypothesis, lungs are not directly affected. First, vagus nerve is affected via carotid sheath. Then, the anterograde transmission of the virus via efferent vagal nerve fibres, which are distributed throughout the lungs, causes interstitial lung fibrosis.[4] Now, let us look the pathophysiology in a step-wise manner.

Pathophysiology in relation to Symptoms

The RCV attaches to the Pharyngeal surface and stays there for 2-3 days heralding the classical symptoms of any URTI- sore throat / odynophagia / fever / bodyache / rhinorrhea caused when the body starts a primary inflammatory response .

Further the patient complains of cough / breathing difficulties / headache and other neurological symptoms / gastric complaints / loss of sense of smell & taste .

The authors hypothesize that after the RCV settles over the pharyngeal musculature it starts its neuroinvasion. The RCV makes its way into the branches of Vagus Nerve which supplies the pharynx similar to the neuroinvasion by the Rhabdovirus . Its spread can also be due to the spread of infection in the parapharyngeal space and then further to the carotid Sheath owing to the proximity of these structures. This causes Neuropathic pain alongwith soft tissue swelling causing severe odynophagia .

The vagus nerve gets affected and hence the anterograde plus the retrograde spread of the neurotropic RCV starts. The symptoms of RCV are similar to that of vagus irritability / excitability in the beginning when the patient starts to have dry cough (without any discernible lung pathology) caused by neuropraxia.

The patient complains of gastric symptoms because of the change in vagal tone. The loss of smell occurs like in any other URTI . However

the loss of taste can be explained by the afflicted vagus nerve nucleus in the Nucleus Tractus Solitarius causing the malfunction of Chorda Tympani. The change in patients' voice can be explained because of the vagal dysfunction supplying the vocal cords. Breathiness, strain & asthenic symptoms of voice increases with the loss in phonatory gap at glottic level .

The Vagus nerve is an important regulator of the parasympathetic system. The anterograde spread of RCV causes the peripheral nervous system (PNS) hypoactivity like the bronchial hyper-stimulation and tachycardia. The lung suffers from the neuronal degeneration of the vagus nerve by the RCV. The pulmonary alveoli supplied by vagal nerve fibres start to die causing the typical COVID LUNG pulmonary interstitial fibrosis.[5]

The sympathetics take over causing overstimulation of heart and lungs manifesting as tachycardia and tachypnoea. The nuclei of Respiratory centres are located in close proximity to the Nucleus Tractus Solitarius hence breathing patterns are prognostic indicators for severity of the disease.

The retrograde spread further causes neurological symptoms like dizziness, vertigo, headache, seizures. Features of encephalitis / meningitis sets in at later stages along with the loss of mental functions /cognitive ability indicating advanced retrograde spread of RCV.

In parallel to the ongoing symptoms the inflammation of vagus nerve by RCV first activates the proinflammatory cytokines. These detect the neural inflammation and alert the body for massive response later in course of disease referred to as cytokine storm. Moreover, the inflammmed nerve in carotid sheath causes the stasis and thrombophlebitis in the Internal Jugular Vein (similar to Lemieres Syndrome). The most common diagnostic indicator is D-Dimer . This causes the coagulation factors and blood parameters to get deranged and sets in the sequalae for disseminated intravascular coagulation (DIC) and multiorgan failure.

Viral Load

The RCV creates a viral Load just like any other virus eg . Human immunodeficiency virus (HIV), Epstein Barr virus (EBV). Just like EBV titres in nasopharyngeal carcinoma (NPC), the RCV affects those individuals more who have low immunity or have less vagal tone. The RCV affects men more than women , adolescent boys > girls due to the drastic fall in nerve Growth factors (NGFs). Men who are in strong romantic relationship <1 yr have constant production of NGF thus are less likely to fall prey to RCV.[6] Women have low levels of nerve growth factors (NGF) and maintain this saturation throughout except during menstruation.[6]

Stages of the disease

Based on clinical symptoms (Progressive Disease)

Stage 1 – Day 0 to Day 3
- Prodromal symptoms - Flu Like illness
- (Dry Cough / Fever / Body ache / Gastric complaints
- Proinflammatory markers released
- Humoral immunity response sets in

Stage 2 – Day 3 to Day 7
- Neuroinvasion , Neuronal injury progressing with increasing Viral Load
- Worsening of symptoms (Wallerian Degeneration)
- Lung Fibrosis starts , SpO2 decreases
- Tachycardia with minimal Heart Rate variability
- Laryngeal palsy (Change In character of voice)
- Sympathetic system compensates by Bronchial & Cardiac overstimulation
- Coagulation factors affected (onset of IJV thrombophlebitis)

Stage 3 – Day 7 to Day 14
- Peak of neurovirulence , Viral Load highest
- Brochospasm and Laryngeal spasm causing Stridor
- Covid lung with extensive pulmonary fibrosis
- Cardiac fibrillations
- DIC
- Multiorgan Failure
- Death

Stage of recovery - It simply follows the course of Flu like illness.

TREATMENT STRATEGY

"Lavanchal Treatment Protocol "

1. Identifying high risk cases :
- Older Age
- Unvaccinated individuals
- Males > Females
- Any CNS pathology
- Diabetes

2. Pre Exposure Prophylaxis (PEP) :

Individuals are presently undergoing vaccination at a gap of 1 month .The better term for such vaccination is Pre Exposure Prophylaxis similar to the PEP in case of Rabies .Thus reducing mortality and morbidity significantly .

3. STAGE 1 ILLNESS -

i. Post Exposure Prophylaxis –

Patients presenting to the Flu Clinic should be categorized into two categories –

A) Pre Vaccinated – Intradermal Vaccines – reduce dose by 1/10 – antigen presenting cells , cost effective , mass vaccination. Such patients will require only two shots of the Whole Virus Killed Vaccine like Covaxin. The authors propose the Covaxin specifically because of the similar properties of the vaccine to the preparation of Rabies vaccine . Two shots to be given at –

Day 0 – as soon as the prodromal symptoms Appear
" Each prodromal symptom to be considered as COVID infection unless proven otherwise "
Day 3 – three days from onset of symptoms

B) Unvaccinated –
Such patients will require 5 shots of the Whole Virus Killed Vaccine .
Vaccine to be administered on Day 0 ,3 , 7 , 14 , 28

ii . Intranasal spray containing – Antiviral like Viraleze, Fluticasone
iii Tab Neurobion 1 BD

Rest continue same drugs as institutional protocol
Tab Favirapir , Tab Zinc , Tab Vit C , Budecort Inhaler

4 . STAGE 2 ILLNESS –

Do not wait for SpO2 to fall .

I . No Post Exposure Prophylaxis Recommended

Timing is of essence since the Post Exposure Prophylaxis is of no role now . Individuals who are Pre vaccinated are at lower risk than tho who are not .

Ii . Tab Chrysin 1 OD
iii . Tab Favirapir 1800 mg BD (D1)
800 mg BD (D2 – D14)
iv . Tab Prednisolone 60 mg OD * 7 days
Followed by Tapering by 10 mg * 2 days
Start IV Dexa 6 mg OD if Spo2 falling
v Tab Neostigmine 15 mg BD * 07 days
vi . Intranasal spray containing – Antiviral/Fluticasone/Nerve Growth factor
Vii Right Lateral Decubitus positioning > Prone positioning (if SpO2 falling)
Viii Cool air therapy (room temp at 16 degr.ee)
ix . Budesonide inhaler 2 puff BD with Oxygen
x . Tab Neurobion 1 BD + Tab Zinc + Tab Vit C
xi . Anticoagulation therapy

5 . STAGE 3 ILLNESS –

Highest mortality & morbidity

Follows drastic course like Rabies illness but instead of Furious Rabies (80 %) it follows Dumb rabies (20 %)

Mimics Acute stage of Myasthenia Gravis or a neurotoxic snake bite , Aggressive management required Continue all treatments as in Stage 2 with addition of -

1. IVIG –same as in a Snake Bite Case / Myasthenia Gravis exacerbation
2. Fresh Frozen Plasma

3. Intubation Coma – interspersed with sympathetic stimulation
4. Anticholinesterase inhibitors not crossing BBB
Inj Neostigmine 0.3 ug/kg 6 hourly with Atropine / Glycopyrrolate combination
5. Inj Neurobion 1 amp * 3 days
6. Sedate with Midazolam
7. Tracheostomy to prevent death due to Laryngospasm & reduce VAP
8. Cold Water submersion of patient / Cool room / cold ice therapy
9. Intrathecal administration of Nerve Growth Factors
Rt lat decubitus > Prone (esp when intubated)

Iv Dexamethasone / inj Methylprednisolone pulse therapy
Antiviral Injections
Anticoagulation therapy if IJV thrombophlebitis suspected
Avoid Neuromuscular Blockade as much as possible Usage of agents increasing Nerve Growth Factors like 2-DG , Quercitin , Ginkgo Biloba , Gotu Kola , Chrysin , DHA etc .

PROPOSED DIAGNOSTIC CRITERIAS

No need for high profile & intensive tests because it is a clinical disease
For confirmation of disease & complications follow this protocol

1. Any Flu like illness to be considered COVID
Start treatment as Stage 1 illness

1. Patient to undergo HRCT Chest plus CECT/MRI Neck if Stage 2 illness to rule out Lemierre's syndrome (a type of sepsis which is complexed by several thrombus along with thrombus in internal jugular vein)[7]

2. Doppler USG to rule out IJV involvement
3. Test for Myelin Basic Proteins (Oligodendrocyte marker) in CSF
4. Heart Rate Variability as indicator of vagal tone
5. RCV titres testing for every individual
6. Laryngeal electromyography for vagal tone of both sides

CONSEQUENCES OF THE HYPOTHESIS AND DISCUSSION

The core concept of our hypothesis is that the RCV disease is an autoimmune viral disease affecting vagus nerve. We have hypothesized that vagus nerve is a parasympathetic organ. Some case reports on upper respiratory infections by Milan et al also demonstrates involvement of vagus nerve.[8]

We hypothesize that RCV is neurotropic and neuroinvasive similar to other human coronaviruses.[9] There should be no doubt about neurotropism of RSV owing to the similar nature of other human coronaviruses. The anterograde and retrograde transmission of the virus along the branches of vagus nerve produces the cascade of symptoms that occur during the disease course.

Our hypothesis aims at new understanding of the pandemic. If this hypothesis tests to be true, it can introduce new and targeted treatment strategies with better management of moderate to severe cases. Maintenance of vagal tone needs to be emphasized upon. Pre exposure and post exposure prophylaxis can alter the course of the disease. Effectiveness of intradermal vaccination should be considered.

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