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Review Article

Cross Talk between SARS-CoV-2 New Strains and Ischemic Stroke

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Abstract

Coronavirus disease 2019 (COVID-19) is responsible for the global pandemic situation nowadays which caused by novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Through the receptor-binding domain (RBD) it binds to angiotensin converting enzyme 2 (ACE 2) protein which induces the infection having symptoms of fever, cough, dyspnea, headache, sore throat, ageusia, anosmia etc. The infection can be transmitted through respiratory droplets and faecal oral route and by using belongings of infected person and can be diagnosed by RT-PCR, rapid antigen test, chest computed tomography (CT), blood test, chest X-ray etc. The preventive steps are vaccination, wearing mask, proper sensitization and use of immune stimulants with 14 days of quarantine if there is close contact with COVID-19 positive patient. The modern variants of SARS-CoV 2 are B.1.1.7 (UK), B.1.1.207 (Nigeria), B.1.429 (US), B.1.427 (US), B.1.351 (South Africa), P.1 (Japan and Brazil), B.1.525 (UK and Nigeria), 501Y.V2 (South Africa) etc. are developing due to mutation and may increase transmission intensity, severity of disease and pathogenesis. SARS-CoV 2 severity can initiate acute ischemic stroke through a number of mechanism like ACE 2 depletion, coagulative dysfunction, endothelial dysfunction and inflammatory responses. The management of stroke is a major challenge and much complex process. Both patient and health care professional should wear personal protective equipment (PPE) kit. The infected COVID-19 patient goes through cerebral CT, CT perfusion and CT angiography on mobile or well facilitate CT unit situated outside or inside the emergency department. There after the patient shifted to the specific intensive care unit (ICU) for COVID-19 patient with anaesthesia. If the patient is suspect of COVID-19 then first the sample is collected and then the standard stroke management pathways are followed in a separate ICU. If the results come positive then the patient is transferred to that COVID-19 infected patient ICU and if results comes negative then the standard stroke management protocol are followed. This study is based on this COVID-19, new strains of SARS-CoV 2, pathophysiology involved in COVID-19 mediated ischemic stroke with their management.

Keywords: *COVID-19; New Strains, Ischemic Stroke; Management*

Introduction

Coronaviruses are single stranded ribonucleic acid (RNA) genome virus with crown like structure because of glycoprotein spike appearance on its envelop. There are 4 genera of corona virus; 1) α- Coronavirus, 2) β- Coronavirus, 3) δ- Coronavirus and 4) γ- Coronavirus [1,2]. There are total of 6 coronaviruses identified which are linked with human. 4 key structural proteins-coding genes are identified in coronavirus; 1) Spike protein, 2) Envelop protein, 3) Membrane protein and 4) Nucleocapsid protein [3]. A novel coronavirus was firstly informed to World Health Organization (WHO) on 31 Dec 2019 by the Chinese authorities from Wuhan, Hubei province. The coronavirus disease 2019 (COVID-19) is an infection due to the novel virus which is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. The Director-General of WHO, Dr. Tedros Adhanom Ghebreyesus named this infective disease as COVID-19 on 11 February 2020. SARS-CoV-2 is a type of nucleated virus which comes under β- Coronavirus group family [2]. For the activation in host, spike protein

of SARS-CoV 2 utilize angiotensin converting enzyme (ACE 2) as its cell surface receptor [5]. As there were 114 countries involved and exceeded 118,000 cases with more than 4000 demise, WHO announced COVID 19 as a pandemic on 11 March 2020 [6]. Till the end of March 2021, the COVID-19 positive cases are 128 million and the death occurrence is 2.8 million worldwide; where as in India, the positive cases are 12.1 million and death occurrence 162k. The symptoms involved in COVID-19 are fever, cough, dyspnea, headache, sore throat, ageusia, anosmia, rhinorrhea, fatigue, anorexia, myalgias etc. which depend upon the severity of infection [6]. For the diagnosis of COVID-19 the golden tool is RT-PCR by taking sample from nasopharynx or oropharynx. Except this other diagnosis procedures are rapid antigen detection test, blood test (WBC count), chest X-ray, chest computed tomography (CT) etc. can be used depending on the availability and requirements. Infection can mainly transmit between persons via respiratory droplets and faecal oral route. Apart from this infection can be transmitted via belongings of infected person. The evolution phase of COVID-19 is 5 - 7 days but in some cases it has been seen up to 14 days. Thus, the quarantine of 14 days is mandatory [7,4]. The severity of COVID-19 depend upon certain complications like, cardiovascular diseases, diabetes, acute respiratory disorders, coagulopathy, acute liver and kidney injury, laryngeal oedema and laryngitis, ventilation-associated pneumonia, multiple organ failure, septic shock, massive pulmonary embolism with certain neurological complications [4]. Vaccination is only the current precaution for the COVID-19. With this wearing mask, proper sanitization, taking of immunestimulants can protect from infection. Due to mutation a numbers of new strains of SARS-CoV 2 are generating. The current variants may initiate the transmission, severity, pathogenesis of COVID-19. New variants of SARS-CoV 2 are B.1.1.7 (first identified in UK), B.1.1.207 (Nigeria), B.1.429 (US), B.1.427 (US), B.1.351 (South Africa), P.1 (Japan and Brazil), B.1.525 (UK and Nigeria), 501Y.V2 (South Africa) etc. Severe COVID-19 infection can cause acute ischemic stroke, encephalopathy, seizures, headache, cerebral microbleeds, hemophagocytic lymphohistiocytosis, cranial nerve palsies, demyelinating disorders etc [8]. From a number of studies it is confirm that COVID-19 can induce cerebral ischemia through a number of mechanisms like ACE 2 depletion, coagulative dysfunction, endothelial dysfunction and inflammatory responses. The severity of stroke depends upon the infection degree, historical infection, age, sex etc [9]. Acute stroke management in the COVID-19 positive patients is a crucial pathway. The patient taken to hospital where at first the patient and health care professional wear personal protective equipment (PPE) kit. After that the patients goes for CT angiography, cerebral CT and CT perfusion on a mobile or well facilitated CT unit outside or inside emergency department. Then the patient transferred to COVID-19 patients intensive care unit (ICU) with anaesthesia. If the acute stroke patient is suspect of COVID-19 then first the sample is collected with the standard stroke management pathway. If the patient got COVID-19 positive then the patient transferred to that COVID-19 infected patient ICU. If the patient got negative then the standard stroke management protocols are followed [10,11]. In this review we have established a relation between COVID-19 and cerebral ischemia, new varients of SARS-CoV 2 and management of COVID-19 mediated ischemic stroke.

NEW strains of SARS-CoV 2

Several new strains of SARS-CoV 2 are evolving nowadays. They increase transmission, severity and pathogenesis of COVID 19 by mutation. It is supposed that maximum mutations happen neutrally. It is also reported that there is no significant change in virus characteristics [12]. As these variants bind to ACE 2 receptors and there is no significant change in properties, these may also involve in the pathogenesis of stroke. Different strains of SARS-CoV 2 are given in table 1.

Variant	Mutation	First Identification
B.1.1.7	N501Y, 69-70 del, P681H	UK
B.1.1.207	P681H	Nigeria
B.1.429	14205V, D1183Y, S13I, W152C, L452R	US
B.1.427	14205V, D1183Y, S13I, W152C, L452R	US
B.1.351	N501Y, K417N, E484K	South Africa
P.1	N501Y, E484K, K417T	Japan and Brazil
B.1.525	E484K, F8884	UK and Nigeria
501Y.V2	N501Y	South Africa

Table 1: *List of SARS-CoV 2 variants, their mutation site and first identified country.*

Ischemic stroke characteristics in covid-19 positive patients

Though few neurological symptoms occur in COVID-19 infected patients, some current report shows that a remarkable percentage of patient's shows neurological manifestation. Acute ischemic stroke (AIS) is one of the neurological disorders due to affected by SARS-CoV 2 infection but the occurrence is less. Current data shows that persons affected by COVID-19 become develop AIS. Oxyley., *et al.* informed that 5 COVID-19 positive patients in city hospital of New York having 2 weeks of large vessels occlusion type of stroke, showing either no or rare risk factor for stroke. The AIS degree is about 5% in COVID-19 positive patient as per a latest study from Wuhan. From a latest international publication, stroke occurrence in COVID-19 patient found to be 1.3%. Different characteristics feature of stroke which appears in COVID-19 positive patients includes anosmia, ageusia, ataxia, visual disturbances, delirium, confusion, paralysis etc [13].

Pathophysiology

ACE 2 depletion

ACE 2 is a protein on the surface of many cells including heart, lungs, blood vessel. ACE 2 is a vital element in regulating blood pressure. The role of ACE is to convert angiotensin 1 into angiotensin 2. ACE 2 breaks angiotensin II into molecules to counter its side effect and thus helps in their regulation. Role of angiotensin II is to increase BP, inflammation, blood vessel damage. In relation to COVID 19, angiotensin II causes inflammation and death of alveoli. These effects are reduced by ACE 2. When COVID virus binds to ACE 2, it prevents ACE 2 from performing its normal function to regulate angiotensin II. Thus ACE 2 function is inhibited which leads to tissue injury [14]. Entry of virus in host cell is primary step of infection. A spike glycoprotein on viral envelope can bind to specific receptors on host cells. Virus can affect only those cells which have an ACE 2 which proves that ACE 2 is a specific receptor of corona virus. ACE 2 also regulates vascular auto regulation and cerebral blood flow. So this depletion directly interlinks to ischemic condition and may cause cerebral ischemia as shown in figure 1 [15].

Coagulative dysfunction

Approximately half of total COVID 19 patients developed symptoms of coagulopathy. It serves as distinctive feature of COVID 19 disease and also called as sepsis induced coagulopathy [14]. It is characterized with increased levels of D dimer, prothrombin time prolongation, thrombocytopenia with a decrease in fibrinogen level. These coagulative pathway modifications, elevation of D dimer with fibrinogen collectively result in thrombosis increment. It has a direct connection to inflammatory action initiation. Following infection there occurs activation of monocytes and endothelial cells leading to cytokine release and finally intravascular coagulation formation along with expression of von will brand factor [16] COVID 19 initiate misbalance among ACE 2 and angiotensin II receptors and it leads to formation of platelet tissue factor (TF of Factor III) in platelets as well as macrophages. This TF then interacts with Factor VII which leads to extrinsic coagulation system activation [8]. TF also initiates fibrin formation, thrombogenesis and inflammatory cell production [17,18]. Thus, this is a key pathogenesis of cerebral ischemia as shown in figure 1.

Endothelial dysfunction

Endothelium dysfunction is a key pathogenesis which contributes to SARS-CoV 2 associated cerebral ischemia. Through the ACE 2 protein, SARS-CoV 2 acts on endothelial cells. There are mainly two mechanisms which are involved in COVID 19 mediated cerebral ischemia. The first one is extrinsic coagulation system activation. A misbalance between ACE 2 and angiotensin II receptors due to COVID 19 results in formation of TF in platelets and macrophages and that TF causes extrinsic coagulation system activation, fibrin formation, thrombogenesis and inflammatory cell production which are the key pathogenesis for cerebral ischemia [17,18]. The second one is nitric oxide (NO) insufficiency. NO is a major vasodilator which is produced from endothelial cells. SARS-CoV 2 reduces the nitric oxide synthase (NOS) activity, which results in less NO production. So, this NO deficiency leads to decrease in vasodilatory effect. This NO insufficiency

also inhibits the platelets and leukocytes adherence to wall of blood vessel. These phenomenon ultimately causes ischemic stroke as shown in figure 1 [8].

Inflammatory response

The SARS COV 2 virus attacks the host cells via attachment to ACE 2 [8]. After recognising the virus, the epithelial cells of respiratory tract release cytokines such as tumor necrosis factor (TNF) and interleukin-6 that causes accumulation of macrophages and monocytes in alveoli. These cytokines initiate other cellular events which leads to secondary hemophagocytic lymphohistiocytosis [19]. Nucleotide-binding domain (NOD) like receptor protein 3 (NLRP3) inflammasome get stimulated by virus through small viro protein 3a which ease the liberation of virus from infected cell. In cytosol, this multiprotein complex carry out different reactions which lead to cytokine production like interleukin 1β, interleukin 18 and damage associated protein. This NLRP3 may activate plaque variability due to some cellular mediators like macrophages, neutrophils and lymphocytes. COVID-19 mediated inflammations induce prothrombotic events in patients with cardiac activities with previous atherosclerotic plaques. Studies suggest that virally infected neutrophils, T cells and macrophages increase plaque formation. These increased vascular permeability, endothelial interruption, collagen exposuration, adherence of tissue factor with platelet events takes part in thrombogenesis. Plaque in carotid artery having high lipid concentration, bleeding among plaque with monocytic macrophages will cause instability as well as vulnerability to plaque rupture. The enzymes like metalloproteinase and cathepsin promote plaque fragility and cause thromboembolism. Oxidised low density lipoproteins uptake interruption through monocytic macrophages also leads to plaque progression in COVID 19 patients. These pathogenesis leads to cerebral ischemia condition and other neurodegenerative disorder as shown in figure 1 [8,15].

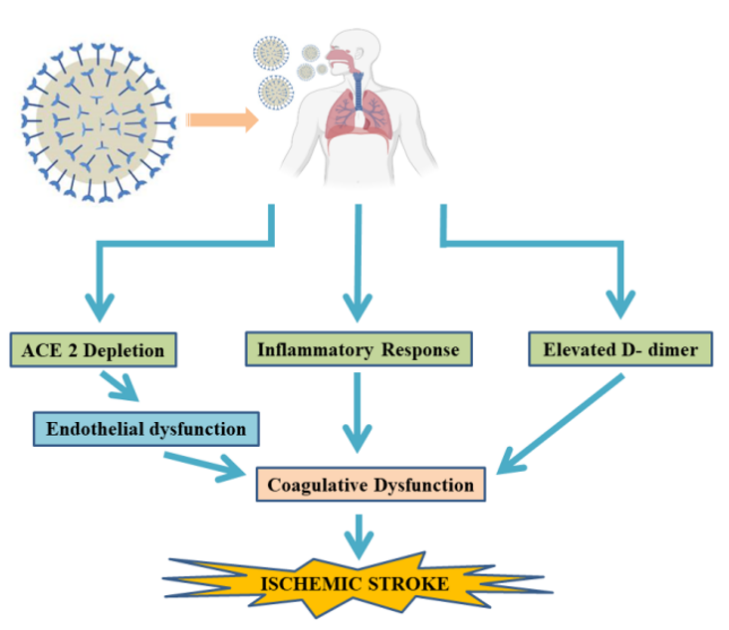

Figure 1: *Pathophysiology involved in COVID 19 mediated ischemic stroke. When SARS-CoV 2 enters into body through nasal or oral route it binds to ACE 2 receptors. Then it depletes the ACE 2 receptor and produce endothelial dysfunction. SARS-CoV 2 also triggers inflammatory response as well as elevates D- dimer. These pathogenesis like endothelial dysfunction, inflammatory response, D- dimer elevation further results to coagulative dysfunction or hyper-coagulation. These phenomenon's are the major pathogenesis of cerebral ischemia.*

Ischemic stroke management in covid 19 positive patients

After emergence of COVID-19 pandemic situations a triage protocol is being activated in emergency department. This helps in assessing patients within a short time after their arrival, assign priorities and transfer them to appropriate place for treatment. Here both patient and health care professional have to wear PPE kit. If patient has confirmed COVID-19 infection, the patient goes through CT angiography, cerebral CT and CT perfusion on a mobile or well-equipped CT unit situated outside or inside emergency department. If the stroke is due to occlusion on large vessel, the patient shifted to other unit for endovascular treatment. At the end of procedure, depending on type of anaesthesia, the patient moved to either infective patient zone or to ICU specialized for patient of COVID-19 infection. If the patient is COVID-19 suspected, first of all nasopharyngeal sample is collected from nasopharynx. At the same time the person goes for CT angiography, CT perfusion and cerebral CT on a mobile CT unit or well facilitated unit situated outside or inside emergency department [10]. Patients considered eligible for i.v thrombolysis will follow the standard procedure or can wait for COVID-19 test result. If report comes negative for COVID-19 the person is shifted to stroke ward. On the other hand if result come positive i.e if patient suffered from COVID-19, patient is moved to COVID-19 infection patient ward. If stroke is due to occlusion on large vessel, the patient is shifted to other unit for endovascular management. If COVID-19 infection test is negative, the patient is either moved to stroke ward or ICU with anaesthesia. If examination of COVID-19 is positive and process is accomplished under conscious state, then patient is shifted to infective patient unit. Further if thrombectomy is accomplished under general anaesthesia, then the patient is shifted to COVID-19 infective patient ICU. Evewry procedures are carried out by wearing PPE kit. When stroke patient does not have COVID-19 suspect cases, then standard acute stroke pathway is followed [11].

Conclusion

SARS-CoV 2 is a novel coronavirus which causes COVID-19, a pandemic. The infection was started in early December of 2019 from Wuhan, China. SARS-CoV 2 attacks ACE 2 by its receptor-binding domain (RBD) and produces different pathogenesis. The major symptoms are fever, cough, dyspnea, headache, sore throat, ageusia, anosmia etc. The diagnostic tests are RT-PCR, rapid antigen test, blood test, chest X-ray, chest CT etc. The transmission of infection occurs through respiratory droplets and faecal oral route and belongings of infected person. So the quarantine of 14 days is mandatory to minimise the spreading of infection. Vaccination, mask wearing, use of sanitizer and taking proper immune stimulant are the protective and preventive steps against COVID-19 infection. Nowadays there are new strains of SARS-CoV 2 which are increasing the transmission, severity and pathogenesis by the mutation without any significant changes. The major strains are B.1.1.7 (UK), B.1.1.207 (Nigeria), B.1.429 (US), B.1.427 (US), B.1.351 (South Africa), P.1 (Japan and Brazil), B.1.525 (UK and Nigeria), and 501Y.V2 (South Africa) now spreading over worldwide. COVID-19 severity can cause acute ischemic stroke, encephalopathy, hemophagocytic lymphohistiocytosis, seizures, headache, demyelinating disorder and neurodegenerative disorder. Numbers of studies suggest that the severity of SARS-CoV 2 can induce AIS in patient with COVID-19 infection. The major pathogenesis involved in the pathogenesis of stroke in COVID-19 positive patients are ACE 2 depletion, coagulative dysfunction, endothelial dysfunction and inflammatory responses. These pathogenesis may increase the severity of ischemic stroke depending upon the degree of infection, historical infection, age, sex etc. Stroke management in COVID-19 positive patients is a key challenge which follows different and complicated pathways. After arrival of the patients both patients and health care professional wears PPE kits. If the patient is COVID-19 positive then patient undergo CT angiography, CT perfusion and cerebral CT on a mobile or well-equipped CT unit situated outside or inside emergency department and further transferred to the specific ICU for COVID-19 patient. In case of COVID 19 suspension, first the samples are taken and further the standard stroke protocols are followed in another specific ICU. If the patient is COVID-19 positive then it is transferred to particular ICU for COVID-19 patient and if negative then the standard stroke protocol are followed. In this study a systemic review on new strains, ischemic stroke pathogenesis in COVID-19 disease with their management are enumerated.

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