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Review

COVID-19: Understanding a New Disease through Global Efforts

COVID-19 : Global Bir Çaba Olarak Yeni Hastalığı Anlamak

Arzu Akçay*, Kubilay Kınoğlu, Ayşe Özgün Şahin

Abstract: **Objective**: COVID-19, the disease caused by the novel coronavirus SARS-CoV-2 which was first reported in Wuhan, China in December 2019, is seen to have left its mark in the history with a global pandemic. As a novel member of the coronavirus family, SARS-CoV-2 represents a new kind of disease in regard to viral pathogenesis and tissue changes. To comprehend the pathogenicity of the virus totally, one has to follow the pathways which a virus travels and inflicts damage through. What starts out as a simple fever and coughing carries the potential to lead to shock, multi – organ failure and death even in the most unsuspected of cases. When faced with a challenge as contagious, deadly and widespread as this, one should put all the efforts that they have in order to overcome this obstacle. In the case of COVID-19 this cumulative effort has shaped itself into a globalized form. In an attempt to see the wider picture as to the whole pathogenesis of COVID-19, the medical and scientific society should recall the importance of a fundamental discipline, namely, autopsy. Even though, conducted in small numbers at the time, autopsies of COVID-19 cases have provided the literature with many important information. The role of autopsy in understanding disease, the immune system and pathogenesis is one that should not be disregarded and conversely, should be further developed and praised. The same ideology would apply to COVID-19 and any further pandemics to come.

Keywords: COVID-19, Pandemic, Pathogenesis, Autopsy

Öz: **Amaç**: Aralık 2019 tarihinde Çin'in Wuhan kentinde ortaya çıkan, yeni tip bir Korona virus olan SARS-Cov2'nin etkeni olduğu hastalık (COVID-19), tüm dünyayı etkisi altına alan bir pandemi ile insanlık tarihine damgasını vurmuş görünmektedir.

Korona virus ailesinin en yeni üyesi olan SARS-CoV-2 gerek viral patogenezi, gerekse doku düzeyinde gösterdiği değişiklikler açısından özellikle SARS-CoV ile benzerlik gösterse de yepyeni bir hastalık tablosu ortaya koymaktadır. Virüsün sahip olduğu patojeniteyi kavrayabilmenin ilk koşulu virüsün hareket ettiği ve hasar verdiği yolakları takip etmekten geçer. Basit bir ateş ve öksürük olarak başlayan bir durum, şok, multiorgan yetmezliği ve hatta en beklenmedik vakalarda ölüme sebep olabilir. Böylesine bulaşıcı, ölümcül ve genele yayılmış bir zorluk ile karşılaşıldığı taktirde, eldeki bütü imkanlar en iyi şekilde değerlendirilmelidir. COVID-19 isimli hastalığın durumunda ise bu çabalar birikmiş bir hale gelerek, evrensel bir şekle bürünmüştür. COVID-19 hastalığının patogenezinin anlaşılmasında, tıbbi ve bilimsel toplulukların otopsi disiplinin önemini hatırlamaları gerekmektedir. Az sayıda gerçekleştirilmiş olmalarına ragmen, COVID-19 otopsileri, literature oldukça önemli bilgiler kazandırmışlardır. Hastalığın, bağışıklık sisteminin ve patogenizin anlaşılmasında otopsinin rolü göz ardı edilmemeli, tam tersine, daha çok gelişitirilmeli ve el üstünde tutulmalıdır. Aynı düşünüş tarzı, gerek COVID-19 gerekse gelecekteki pandemiler perspektifinde oturtulmalıdır

Anahtar Kelimeler: COVID-19, Pandemi, Patogenez, Otopsi

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Assoc. Prof. Dr. Arzu Akçay: MD, PhD, Pathology Spec, Forensic Medicine PhD. Council of Forensic Medicine, İstanbul
E.mail: arzuakcay12@gmail.com
ORCID: https://orcid.org/0000-0001-8343-1153

Dr. Kubilay Kınoğlu: MD, Forensic Medicine Spec, Council of Forensic Medicine, İstanbul
E.mail: dr.kubilaykinoglu@gmail.com
ORCID: https://orcid.org/0000-0002-3972-559x

Dr. Ayşe Özgün Şahin: MD, Pathology Spec, Council of Forensic Medicine, İstanbul
E.mail: aozgunsahin@gmail.com
ORCID: https://orcid.org/0000-0002-6149-8397

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* Corresponding Author

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Introduction

COVID – 19, the disease caused by the novel coronavirus SARS-CoV2 which was first reported in Wuhan, China in December 2019, is seen to have left its mark in the history with a global pandemic. The family of coronaviruses includes a large number of zoonotic viruses which cause infections in both the upper and lower respiratory tract, gastrointestinal system, central nervous system and hepatic cells of humans and vertebrates (1-4)

The human dominant ecosystem, migrations, increasing human dynamism and human – animal contact, are to be considered as unimpeachable factors of risk when it comes to the occurrence of various viral infections. The coronaviruses which have caused similar outbreaks in the past hundreds of years, have adapted to the human organism and are known to cause mild, seasonal, community acquired infections in general. (1,2,4) However, epidemics caused by the novel coronaviruses SARS (Severe Acute Respiratory Syndrome) – CoV, MERS (Middle East Respiratory Syndrome) – CoV and SARS – CoV2 demonstrate the potential of these newly evolved viruses in causing drastic risks in regard to global health **(2).** SARS – CoV2, much like SARS – CoV, binds to the integral membrane protein ACEII (Angiotensin Converting Enzyme II) through the receptor binding region of the spike glycoprotein and diffuses through the cellular membrane, thereby, SARS - CoV2 regards all ACE II expressing cells as potential hosts (5-7)**.** Even though there exist many similarities between SARS – CoV2 and SARS – Cov, in regard to viral pathogenesis and tissue level manipulations, SARS – CoV2 presents a new case of sickness. Concerning the active treatment of patients and the research conducted on vaccines and pharmaceuticals, it has become a global effort to understand COVID – 19.

Viral Pathogenesis

Viral infections occur from the binding of viral agents to specialized receptors, localized throughout the cellular membrane. Therefore, receptor recognition is a key point in the determination of tissues and cells which, a virus will infect (8).

SARS – CoV2 is a positive sense single stranded RNA (+ssRNA) virus in the family *Coronaviridae* and the genera *Betacoronavirus,* that is reported to infect target cells through recognizing the angiotensin converting enzyme – II (ACE II) which is located on the membranes of mammalian cells. (7,8) Transmembrane Protease Serine II (TMPRSS2), Cathepsin L and B (CTSL/B) have been reported to act as mediators of viral diffusion through the

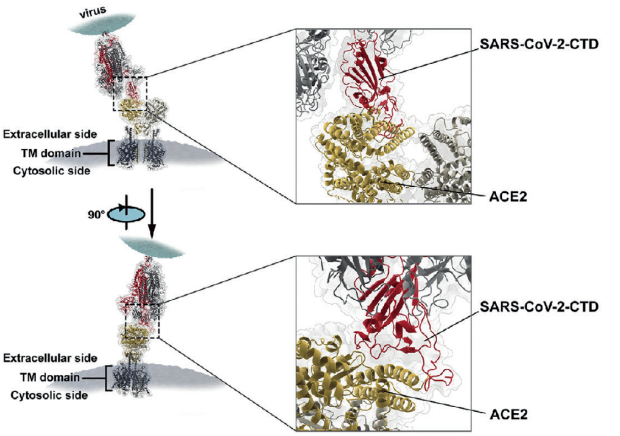

Figure 1. SARS-CoV 2, binds to the integral membrane protein ACEII through the receptor binding region of the spike glycoprotein and diffuses through the cellular membrane

cellular membrane. (6,9) The coronavirus SARS-CoV is known to infect cells through ACE II affinity as well, however, SARS – CoV and SARS – CoV2 show very noteworthy antigenic differences (10). The C – terminal domain, located on the spike protein of the SARS – CoV2, binds to human ACE-II, much like SARS – CoV, and infiltrates the cell. However, the distinct amino acid sequencing observed within the ectodomain of the SARS-CoV2 spike protein revealed that SARS-CoV2 binds to ACE-II with almost 10 to 20 times the affinity of its relative SARS – CoV. This high capacity of receptor binding eases the infiltration of the cell and possibly increases the rates of human to human infections. Type 1 and type 2 pneumocytes, macrophages, gut enterocytes, endothelial, corneal epithelial cells, cardiomyocites, pericytes, olfactory sustentacular cells, hepatic and renal epithelial cells are common cells with ACE II expression and are therefore, common spots of replication for the virus (6) The respiratory system, cardiovascular system, central nervous system, gastrointestinal system and the urogenital system are discussed to be important bodily systems which are capable of being affected by COVID – 19.

COVID – 19 and Acute Respiratory Distress Syndrome

The droplet transmitted SARS – CoV2, can generally infect ACEII carrying type I and type II pneumocytes, macrophages and endothelial cells. Patients, proven to carry SARS – Cov2, show symptoms in the lungs both in clinical and radiological fashion. Pneumonia, along with fever and coughing, is the most common clinical condition seen in SARS – CoV2 infections. 20 - 30% of the COVID – 19 induced pneumonia cases, require mechanical ventilation procedures for their treatment. SARS

– CoV2 shows significant resemblances to both SARS – CoV and MERS – CoV, as the viral interstitial pneumonia is complicated even further with the development of ARDS (11). Research conducted by Richardson et.al. reported that out of 2634 cases, 14.2% required intensive care treatments while 12.2% needed invasive mechanic ventilation procedures. It is also reported that 21% of the treated patients were died. (12) The alveolar epithelial and endothelial damage caused by SARS – CoV2, induces a strong inflammatory response and results in ARDS, which is a systemic condition rather than a lung specialized pathology. Under histopathological borders, ARDS is shown with Acute Lung Injury / Diffuse Alveolar Damage (ALI/DAD). Therefore, the interstitial and peribronchial mononuclear infiltration caused by COVID – 19 based viral pneumonia, is accompanied by ALI/DAD originated alveolar and septal edema, fibrin exudation and the formation of the hyaline membrane within the alveoli necrotic debris, micro thrombosis formation within the interstitial capillary lumens, change in fibroblastic response according to the phase of the infection and alveolar epithelial proliferation (13). Since the beginning of the pandemic, even if in low amounts, core biopsies and limited or full autopsies are conducted to provide data as to the histopathology of the disease. However, the number of autopsies remains to be insufficient, as the procedures are hindered in order to protect physicians, who conduct autopsies, from the virus. The first data of ALI/DAD were acquired by Tian et.al. (14) from the lobectomy of two SARS – CoV2 diagnosed lung cancer patients. A procedure conducted by Carsana et.al., which included the autopsies of 38 COVID – 19 patients, reported the differences in the lung tissue to be correspondents of ALI/DAD and that broad microvascular thrombosis was detected. In this work, SARS – CoV2 particles were shown to be present within the alveolar epithelial cells ultra – structurally (15). Varga et.al. have presented proof in two COVID – 19 autopsy cases, through electron microscopy, that there existed viral particles within the vascular endothelium and glomerular capillary endothelium in addition to the mononuclear cellular infiltration seen in lungs, hearth, kidneys and the gut. Through this finding, they have also reported that endothelial dysfunction caused by endolitis may play a part in the pathogenesis of the disease (16). In a work where Barton et.al. evaluate two COVID – 19 full autopsies, it is reported that only one of the cases that was PCR verified through the nasopharyngeal samples, contained ALI/DAD symptoms and the changes caused by the viral pneumonia. The cause of death for the other case is determined to be the aspiration pneumonia. The evaluation of the information that is acquired from this work concluded death from COVID – 19 is quite different from death in the presence of COVID – 19 (17). The information that we have, shows that the virus SARS – CoV2 causes multiple organ failure – shock and death, through infecting ACE II carrying respiratory epithelial and endothelial cells and generating a strong systematic inflammatory response (SIRS) (18) Severe COVID – 19 patients, show high concentrations of CRP, Ferritin and D – Dimer; in addition, the neutrophil/lymphocyte ratio shifts in the favor of neutrophils. Lymphopenia too is another very important finding. The cytokine and chemokine profiles of these patients resemble the ones seen in Cytokine Secretion Syndrome/Macrophage Activation Syndrome. This gave birth to the hypothesis that the increase of IL – 6, IL – 7, TNF, CCL2, CCL3, CCL10 and IL2R alpha being the cause of the uncontrolled activation of the mononuclear phagocyte compartment and COVID – 19 related hyperinflammation. (19)

The natural immune response, that is generated against viruses, starts with the receptors present on the membranes of the immune system cells, recognizing the exogen pathogen (PAMP) damage patterns. Primary pattern recognizing receptors are transmembrane Toll – like receptors (TLRs), cytosolic (PRRs) and nucleotide bound oligomerization domain like receptors (NLRs) (20). Under normal conditions there exists M1 phenotype macrophages within the alveoli, however, when the inflammation is initiated M2 phenotype macrophages and neutrophils migrate from the bloodstream to the lung (18,20,21) Macrophages, monocytes and neutrophils take part in the secretion of proinflammatory cytokines such as proteases, reactive oxygen derivatives, eicosanoids, phospholipids, IL – 1, IL – 6, IL – 8, IL – 12 and TNF – α (20) . The generated cytokine response and the migrating inflammatory cells further exaggerate the epithelial and endothelial damage. (20,22). The activation of the coagulation system due to the generation of the inflammatory response is a highly important component of ARDS pathophysiology. Endothelial damage exposes subendothelial collagen and allows expression of the tissue factor (TF) and the Von Willebrand Factor (VWF) on the endothelial cell surfaces, which in return activates the coagulation system. TF builds the basis for the formation of the micro thrombosis through converting prothrombin into thrombin and fibrinogen into fibrin (23,24). In the absence of endothelial damage, however, activation of coagulation is initiated through the recognition of TF expressing monocytes by the endothelial cells. A strong macrophage response and the accompanying activation of the coagulation system may be the reason as to the occurrence of COVID – 19 related hyperinflammation. This

could most probably have the potential to bring along a phase of tissue repair and fibrosis (19).

Interferons are cytokines which are known for their antiviral effects. There exist three main families of interferons, namely, Type I (IFN alpha/beta), Type II (IFN gamma), Type III (IFN delta). Once they are secreted from the infected cells, newly synthesized interferons bind to their respective receptors and initiate the JAK/STAT pathway (25). Through this pathway, interferon stimulated genes (ISG), such as ACE II, are activated (26). These genes not only work in the synthesis of antiviral effectors and molecules but also regulate interferons either positively or negatively (4). A postponed or faulty interferon response would make it harder for the virus to be contained while increasing the chances of tissue damage (19).

Cardiovascular System and COVID-19

SARS-CoV 2's affinity for ACE II on mammalian cells, makes possible to infect cardiac myocytes and pericytes, in addition to pneumocytes . The presence of an underlying comorbid disease, the possibility of the development of severe COVID – 19 pneumonia and death increases. Huang et al(11) have founded, hypertension (%15), cardiac diseases (%15) and diabetes mellitus as comorbid diseases (%20) in 41 patients, whom they treated at the hospital. Richardson et al. (12) in the series of 5700 cases they followed and treated at the hospital, have reported that they found hypertension (56,6%), obesity (41,7%) and diabetes mellitus (33,8%) as prominent comorbid diseases. Although the causes of comorbidity are similar, it is clear that their frequencies vary significantly with according to the populations. In addition to the presence of comorbidity, age, systemic inflammation, hypercoagulability and immobilization comprise important risk factors for cardiac complications in COVID-19. Arryhtmias, myocarditis, myocardial infarction and thromboembolism are the main cardiovascular pathologies anticipated in COVID-19 (27). It has been reported that patients with COVID - 19 consulted the hospital with symptoms such as chest pain, dysrhytmia, and acute left heart failure in addition to fever, cough and weakness (28-30). The most common cardiac complication in infections of SARS-COV2 are arrhytmias. Wang et al. have reported an incidence of 16.7% in the occurrence of arythmias in hospitalized patients , whereas, the rate of the symptoms increased up to 44.4% in those who required intensive care (30) In addition, the information acquired from past works concerning SARS - CoV, MERS - CoV and Influenza, could lead to the conclusion that these forms of viral infections display signs of cardiac arrhythmias as well (31-34). Yu CM et al. have reported the sighting of sinus tachycardia in 72% and sinus bradycardia in 14.9% of total SARS CoV cases (35). Hypoxemia and ischemia seen in severe COVID-19 pneumonias can be involved in the arrhythmia pathogenesis by disrupting the electrical activity of the myocardium. Increased cytokine release, myocyte damage and electrolyte imbalance have the potential to cause arrhythmias. Regarding the cardiac conduction system, direct viral infection and lymphocyte mediated immune damage are discussed to be the reasons as to the provocation of arrhythmias (36, 37).

According to the Chinese National Health Commission (NHC) 11.8% of patients ,who died from COVID-19, were diagnosed with myocardial damage affiliated high levels of Troponin I during the follow ups(38). It has been reported that myocardial damage presented with high troponin levels, varied between 7-17% in hospitalized patients while this ratio increased to 22-31% in patients which were treated intensive care units.(11, 29, 30). Furthermore, viral load studies and clinical findings mostly indicate to the presence of myocarditis in these patients. However, myocarditis has been histopathologically proven in only one full autopsy case and has been defined as fulminant myocarditis.(39). In addition, myocarditis has not yet been detected in most limited or complete autopsy studies(39-41). It is deemed necessary, to conduct a lot more COVID - 19 related autopsies if the myocardial damage pathogenesis is to be understood to the full extent.

Myocyte damage may be caused from the direct infection of the cardiomyocyte, an enhanced immune response or ischemia based on microvascular damage which is originated from an infection in the endothelium or the pericytes. The binding of SARS - CoV2 to the integral membrane protein ACE II, prohibits the cleavage of Ang II into Ang 1 - 7. The increasing concentrations of Ang II induces the secretion of cytokines and is thereby discussed as one of the possible means of cytokine mediated myocyte damage (42).

Heart failure is a common manifestation for patients of COVID -19. Studies have reported that 23-24% of patients consult to the hospital with symptoms and signs of acute heart failure (29, 43). Zhou et al have presented that the mortality in patients with heart failure tends to be higher (29). The discussion regarding the origin of the heart failure should be given the utmost importance as the origins of the condition should be determined to be either viral myocarditis or the decompensation of the underlying heart failure (44). Therefore, there exists a great need for any autopsies which are to be conducted in this area (45).

Acute coronary syndrome is another pathology that results in Tn elevation, which in return, provides ST segments and T wave abnormalities in the ECG procedure, much like a case of myocarditis. This situation, makes it a lot more difficult to conduct a differential diagnosis (46-48). It should be remembered that the increase in metabolic demand ,due to the systemic inflammation, can cause acute myocardial infarction in patients which have underlying coronary artery diseases (49, 50). In addition, excessive release of cytokines has the ability to rupture the atherosclerotic plaques (51, 52). Damaging endothelial cells may cause endothelial dysfunction and therefore lead to acute myocardial infarction (53, 54).Therefore, acute myocardial infarction is an expected pathology in COVID-19 disease.

The endothelial and microvascular damage, inflicted by the cytokines, possess the ability to induce an increase in the permeability of the vessels, vasospasm and a decrease in the cardiac perfusion (55) The microvascular damage mechanism can explain the relation between COVID-19 and Kawasaki disease with small-medium vessel involvement particularly in pediatric group (56-58). Additionally, the acute renal damage, diagnosed in some Covid -19 patients, is thought to be originated from the microangiopathic changes seen in the glomerular capillary tuft (16,29,59).

The number of acknowledgements regarding the increase in the number of thromboembolic complications, seen in COVID - 19 patients, has been increasing gradually. Hypercoagulability, old age and immobility during the phase of intensive care which accompany the hyperinflammation, increase the risk in development of thrombosis and embolisation (60,61).

Drugs Used in the Treatment of COVID-19 and Cardiovascular Complications:

There are many drugs which are used in the Covid - 19 treatment modality, many of which are primarily antihypertensive, antiarrhythmic and anticoagulant drugs. In addition, many antiviral (Remdesivir, ribavirin, Lopinavir / ritanovir) and antimalarial (Choloroquine, hydroxychloroquine) drugs, antibiotics (Azithromycin), corticosteroids and biological drugs (tocilizumab) are included in the treatment.

Chloroquine and Hydroxychloroquine can lead to electrolyte imbalance and QT prolongation by disrupting the intracellular pH (62, 63). HCQ is hypothesized to prolongate the action potential through its interaction with ion channels which are regulated through hyperpolarization, namely funny current ion channels, and L - type Ca++ channels. (64). They are also known to interact with antiarrhythmic drugs.

The drugs Lopinavir and Ritonavir are known to cause cardiac side effects through the elongation of the QT and PR intervals (65). Furthermore, this drug has been recorded to react with anticoagulants (66). Based on the relation of SARS - Cov2 with the ACE II receptors, those who have administered ACE inhibitors are expected to experience a higher viral pathogenicity due to the upregulation of the ACE II receptors (67).

Central Nervous System and COVID – 19

Due to structural and functional damage that they inflict on the nervous system, viral infections are known to be responsible in the occurrence of severe central nervous system conditions, such as encephalitis, toxic encephalopathy and demyelinating disease (68). Pathogenesis of SARS – CoV2, regarding the central nervous system, resembles those of the other novel coronaviruses MERS – CoV and SARS – CoV (69,70).

The sighting of severe neurological symptoms that require urgent medical attention, such as epileptic seizures, impaired consciousness and acute cerebrovascular disease, other than mild clinical symptoms, like headaches, dizziness, nausea – sickness and partial or full loss of smell and taste for instance, in patients diagnosed with COVID – 19 sparked the discussion regarding the effects of SARS – CoV2 on the nervous system and their similarities between SARS – CoV and MERS – CoV. The procedure conducted by Mao et.al., which includes 214 COVID – 19 patients who have been molecularly verified and have ARDS symptoms, indicate that 78 of the patients (36.4%); show central (24.8%), peripheral (8.9%) and skeletal system (10.7%) symptoms which coincide with neurological findings, while severe COVID – 19 pneumonia is accompanied with neurological symptoms in 40 (45.5%) of 88 (41.1%) total patients (71). Chen et.al. has reported that 9% of 99 COVID – 19 pneumonia patients had symptoms of confusion while %8 had headaches (72). In research conducted by Li et.al. 22 of 183 (12%) child patients who show acute encephalitis were reported to be anti – Cov IgM positive (73).

Based on the ability of SARS – CoV2 to create similar symptoms as the past coronaviruses MERS – CoV and SARS – CoV, it is discussed that the same neurotropic mechanisms may be put to use by the given examples (74,75). Due to ACE II present within the glial cells and the neurons, they are discussed to be potential targets for SARS – CoV2. Therefore, the virus is believed to inflict neurological damage through both viral impact and the immune response of the host organism (76).

The Neuroinvasion Mechanisms of SARS – CoV-2

Direct Viral Effect

SARS – CoV2 is thought to reach neuronal tissues through two fundamental mechanisms, namely hematogenous spread (viremia) and transsynaptic spread (neuronal retrograde) and as a consequence, cause direct viral damage.

Because the hematogenous spread of the virus induces the secretion of Interleukins and a variety of cytokines, the permeability of the blood brain barrier increases. Through this pathway, the virus is believed to cause direct neuronal damage. Past works on SARS – CoV displayed the presence of viral particles within the cerebrospinal fluid of the patients. Consequently, SARS – CoV2 was expected to be able to pass through the blood – brain barrier as well (76,77). Proving this, Zhou et.al. reported the presence of SARS – CoV2 in the cerebrospinal fluid of a 56-year-old patient (78). Furthermore, Moriguchi et.al. have diagnosed the presence of SARS – CoV2 in a 24-year-old patient with a negative nasopharyngeal swab test, who showed signs of impaired consciousness and convulsion (79). In addition, Duong et.al. reported a 41 – year – old female patient who showed no signs of respiratory symptoms, however, had isolated meningoencephalitis findings (80). The slow circulation of the virus within the microcirculatory system, is considered to ease the binding of the virus to the ACE II carrying capillary endothelial cells. Therefore, with the occurrence of endothelial damage due to the viral particles, an endothelial rupture based cerebral hemorrhage has the possibility to occur before any neuronal damage (77).

Trans – synaptic spread is discussed to result in a partial (hyposmia) or total loss of smell (anosmia) due to its pathway which runs through the olfactory neuron by basing itself to the cribriform plate of the ethmoid bone. In addition, due to the presence of ACE II within the neuronal cells and the quick initiation of the viral replication cycle, the virus is expected to cause neuronal damage via demyelination before any signs of inflammation show in the early stages (77). Past experiments conducted on animals show that the human CoV is capable of making its way up to the dorsal nuclei in the brainstem and the olfactory nuclei in the pyriform cortex through bipolar epithelial cell mediation and intranasal inoculation (81,82). In 8 SARS autopsies performed by Gu et.al., histopathologic changes in both the cortex and the hypothalamus were diagnosed (74). Examinations conducted on SARS patients in the beginning of the 2000s demonstrated the presence of viral particles within the thalamus and the brainstem. Some coronaviruses are known to have the affinity to spread to the medullar cardiorespiratory system through the trans – synaptic pathway. Therefore, the possibility of neuro – invasion should be regarded in both the treatment and the prevention of COVID – 19 induced acute respiratory insufficiency (83). COVID – 19 autopsies play a key role in understanding the neuro - invasive properties of the virus. Neuronal retrograde transport is also discussed to take place through the vagal neuron extensions in the lung tissue and the sympathetic neuron extensions within the gastrointestinal enteric system. Furthermore, the direct neuronal damage inflicted by the virus has the possibility of inducing neurodegenerative disease at a later stage (84, 85).

Host Dependent Indirect Viral Effects

Host dependent damage mechanisms, which can be classified as hypoxic damage, immune damage, ACE II related damage and other mechanisms, are built on the indirect effects of the virus.

The development of severe hypoxemia in COVID – 19 patients, results in an increase in the collection of acid at the brain through the anaerobic metabolism and consequently, cause a headache due to cerebral vasodilatation, edema and disruption of the cerebral blood flow. The persistence of this condition could lead to the formation of neurologic symptoms such as acute ischemic stroke, due to a pressure build up within the head (86).

The antiviral systemic cytokine response and the secreted local cytokines from the microglia and astrocytes, due to viral stimulation, are discussed to cause inflammation and damage in the brain tissue (76,87). Poyiadji et.al. have reported the sighting of acute hemorrhagic necrotizing encephalopathy symptoms in the radiological examination of a confirmed COVID – 19 patient. Acute hemorrhagic necrotizing encephalopathy, also seen rarely in other viral infections, is believed to be caused from the disruption of the blood brain barrier due to the cytokine storm within the brain (88).

In ACE II related damage mechanisms, the virus increases levels of Ang II within the body. Based on the damage inflicted on the regulatory mechanisms of the blood pressure regulation and anti – atherosclerotic mechanisms of both the central nervous system and the striated muscle tissue, the probability of hypertension and cerebral hemorrhage is considered to increase indirectly (76,89). A work by Conde et.al. reported the sighting of massive intracerebral hemorrhage in a 79-year-old COVID – 19 patient and discussed the reason as to the occurrence of this condition to be either direct vascular endothelial damage or ACE II related hypertension (82).

The lack of major histocompatibility (MHC) antigens in central nervous system cells, necessitates the usage of cytotoxic T cells which, in return, is discussed to induce the apoptotic phase in mature neurons (76, 90).

In conclusion; COVID – 19 is a disease which has not been treated or documented until this recent pandemic. Proper diagnosis, treatment methods and the development of vaccines and drugs, are all possible through a well established understanding of viral structure, virus – human cell interaction and the human immune system. The conceptualization of all this information, relies heavily on the guidance of autopsy practices. Indeed, the increase in the amount of information regarding COVID – 19 since the administration of complete autopsies, should not come as a surprise. Both modern medicine and medicine as a discpiline of sciences have been heavily developed through the fundamentals of autopsy throughout 19th and 20th centuries. Autopsy tells of the diseases of the humankind. Yet once again, autopsy has proven itself as one of the most important circles within the scientific methodology in the light of the current events.

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