SCIENTIFIC ARCHIVES OF DENTAL SCIENCES (ISSN: 2642-1623)

Volume 5 Issue 1 January 2022

Review Article

Challenges of Post Covid Syndrome-A New Menace

Ranjan Sengupta[1]*, Malwika Sisodia[1], Amit Kumar[1], Gaurav Verma[1] and Sudeshna Banerjee[2]

[1]Department of Conservative Dentistry and Endodontics, Mithila Minority Dental College and Hospitals, Darbhanga, India

[2]SSKM IPGMER, Kolkata, India

***Corresponding Author:** Ranjan Sengupta, PGT, Department of Conservative Dentistry and Endodontics, Mithila Minority Dental College and Hospitals, Darbhanga, India.

Received: July 11, 2021; **Published:** December 28, 2021

Abstract

COVID-19 has created a devastating scenario across the globe being the major infectious disease prevailing since 2020 till date. Acute infection due to severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) can appear in varied spectrum of illness, alternating from asymptomatic state to critical life threatening condition. Post-acute covid-19 is thought to be a multisystem disease usually occurring after a comparatively mild illness. Patients mostly complain of fatigue and dyspnea, while others include joint and chest pain after acute COVID-19. Apart from these, specific organ related symptoms principally concerning the heart, lungs, and brain have also been accounted for. Researchers are of the belief that patients who recover from acute SARS-CoV-2 infection will present with certain sequelae in the long run, due to obstinate symptoms, sustained organ dysfunction or possibly due to new syndromes. However, the full gamut of the nature, duration, gravity and severity of post-acute COVID-19 is presently unfamiliar and research is still going on. It is thus clear that the overall incidence of post-acute COVID-19 symptoms and its effect on organ dysfunction remains a matter of concern to the researchers. Further studies are essential and indispensable for proper understanding of post-acute COVID-19 so as to facilitate multidisciplinary methodology to diagnose and treat this unrelated condition.

Keywords: *Post-Acute COVID-19; SARS-CoV-2; ACE2 Receptor*

Introduction

The world has witnessed one of the deadliest pandemic in the history since 2020 wherein, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the pathogen accountable for coronavirus disease 2019 or COVID-19, that has caused morbidity and mortality at an unparalleled gauge across the globe. The world came to a standstill witnessing a complete shutdown of day to day chores of human beings where a virus took over control of human lives [1]. The World Health Organization (WHO) declared the world-wide outbreak of COVID-19 as a pandemic on March 11, 2020 [2]. It has been seen to be a diagnostic challenge and has highlighted the significance of laboratory diagnosis in order to sustain the spread and treat the patients with serious infection. The clinical symptoms like cough, fever, and dyspnea similar to any other respiratory infections are commonly seen in COVID-19 patients [3,4]. However, the long-term effects of COVID-19 is still a subject to be researched and studied upon.

Post-acute covid-19 ("long covid") is considered to be a multisystem disease, often ensuing after a comparatively mild illness [5]. These patients can be categorized into those with serious symptoms like thromboembolic complications and those with a non-specific clinical picture often characterized by fatigue and breathlessness. There appears to be a third category of patients where covid-19 patients with acute illness required intensive care. Greenhalgh R., *et al.* [6] has defined post-acute covid-19 as extending for more than 3 weeks from the commencement of first symptom and chronic covid-19 as prolonging for 12 weeks or so per se. Due to the

several false negative tests and several people do not undertake the test, it can be recommended that a positive test for covid-19 is not an essential condition for diagnosis [6].

Epidemiology

COVID-19 virus, being the main culprit to create a havoc all around the globe has spread precipitously all around after its emergence in Wuhan, China in 2019 [7]. More than 3 lac people are fighting this severe disease in today's time in India, where apprehensions over COVID-19 have encouraged large-scale inhibition strategies at the national, state and local levels [8]. With the advent and progress of the ongoing pandemic since end of 2019 till date, several studies and reports have showcased various pulmonary and extra-pulmonary manifestations affecting different organs amongst various age groups. The geriatric population and patients with co-morbidities have been stated to have a more arduous disease course involving more than one organ system and an increased mortality rate [9]. WHO has documented that the mortality rate of COVID-19 patients is approximately 3 to 5%, while the remaining infected patients mostly recover. In order to minimize human contact transmission, the Government officials around the world have tried to ensure several measures including prolonged lockdown of public places, offices, market areas etc. and implemented various steps to safeguard the safety of the people, like social distancing, sanitization of areas, and self-quarantine rules etc [10].

Pathogenic mechanism

The exact mode of transmission of this virus is unknown. However, recent studies have shown that droplet spread and airborne transmission are two main modes of transmission of the virus [11]. The chief pathophysiologic mechanisms of acute COVID-19 infection could be explained as under:

- Direct viral toxicity.
- Endothelial damage and microvascular injury.
- Immune system dysregulation.
- Stimulation of a hyperinflammatory state.
- Hypercoagulability.
- *In situ* thrombosis and macrothrombosis.
- Maladaptation of the angiotensin-converting enzyme 2 (ACE2) pathway [12].

There exists a correlation and overlap of genomic sequence identity of SARS-CoV-2 (79%) with SARS-CoV-1 and with MERS-CoV (50%). SARS-CoV-1 and SARS-CoV-2 share ACE 2 as the same host cell receptor with few distinguished variances, like higher affinity of SARS-CoV-2 for ACE2 as compared to SARS-CoV-1. This occurs owing to the differences in the receptor-binding domain of the spike protein that helps to mediate the contact with ACE2 receptor. The spike gene in SARS-CoV-2 has shown divergence (when compared to other structural genes), with only 73% amino acid similarity with SARS-CoV-1 in the receptor-binding domain of the spike protein. An additional S1-S2 cleavage site in SARS-CoV-2 facilitates an efficient cleavage by host proteases and assists successful binding. Thus, these mechanisms have led to the extensive transmission and spread of SARS-CoV-2 [13,14].

The hypothetical mechanisms donating to the pathophysiology of post-acute COVID-19 consists of: (a) virus-specific pathophysiologic changes; (b) immunologic aberrations and inflammatory damage due to acute infection; and (c) expected sequelae of post-critical illness. Post-intensive care syndrome (PICS) involves novel and deteriorating physical, cognitive and psychiatric abnormalities. PICS is thought to indulge microvascular ischemia and injury, immobility and changes in metabolic functions during the crucial stages of illness. It has been reported in studies that 25 - 30% of SARS survivors faced secondary infections. These survivors of acute COVID-19 could be subjected to an augmented risk of bacterial, fungal (pulmonary aspergillosis, mucormycosis) or other pathogenic infections. Nonetheless, the secondary infections fail to elucidate the insistent and sustained sequelae of post-acute COVID-19 [1].

Neutrophil extracellular traps (NETs) release or NETosis is a prevailing mechanism wherein, destruction of microbes occurs leading to the death of neutrophils and hence, release digestive granules comprising of neutrophil elastase (NE) and myeloperoxidase (MPO). A guaranteed hallmark of autoimmune process is the concomitant inflammatory release of autoantigens from dying neutrophils. NETosis causes several tissue-specific and systemic autoimmune diseases inclusive of systemic lupus erythematosus, anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, rheumatoid arthritis, anti-phospholipid syndrome and multiple sclerosis

[15]. It is presumed to be the chief reason of severe and fatal evolution of COVID-19 as was put forward by various research reports. Hence, all should be well-organized in order to note a reappearance of a non-infectious inflammatory illness amongst convalescents: the" Post COVID-19 Syndrome" [16,17].

Classification based on clinical symptoms [18]

- **Mild illness:** Mild symptoms (e.g. fever, cough, or change in taste or smell); no dyspnea.
- **Moderate illness:** Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation 94%.
- **Severe illness:** Oxygen saturation < 94%; respiratory rate, 30 breaths/min; lung infiltrates > 50%.
- **Critical illness:** Respiratory failure, shock, and multi-organ dysfunction or failure.

Clinical manifestations

The most common symptoms specified after acute COVID-19 are fatigue and dyspnea, while others include joint and chest pain. Some of the specific organ related symptoms involving mainly the heart, lungs and brain have also been reported. The aforementioned complications could be related to the outcome of direct viral invasion to the tissues that could possibly be facilitated by the presence of ACE-2 receptor, intense inflammation and a strong cytokine storm, associated damage to immune system, hypercoagulable state or a combination of all the above features [19]. The characteristic symptoms that have been reported include dyspnea, fever, tightness of the chest, lethargy or fatigue, sweats with chills, body and headaches, dry cough, sore throat, altered taste and smell sensation, rashes, irritation in the eyes, hearing loss, and difficulty in concentration, loss of memory etc [17]. These reported symptoms could account as following: fatigue (55%), dyspnea (42%), loss of memory (34%), concentration issues (28%), and sleep disorders (30.8%). However, there was no prominent statistical variance in the symptoms between the ICU and general wards patients [20].

The post-COVID-19 syndrome patients can be allocated into Acute (patients with serious sequelae - thromboembolic complications) and Chronic (patients with non-specific clinical symptoms suffering from fatigue and breathlessness) [21].

Post covid-19 clinical manifestations in different organ systems

Pulmonary: Patient complains of dyspnea, reduced exercise capability and hypoxia. Features like reduced diffusion capacity, obstructive pulmonary function, ground-glass opacities and fibrotic changes have been seen in the COVID-19 patient. The following diagnostic protocols that needs to be followed to assess the progression of pulmonary disease, include home pulse oximetry, 6MWTs, PFTs, high-resolution CT of the chest and pulmonary angiogram as clinically applicable [1].

Hematologic: Studies have shown that there are thromboembolic events in about < 5% post-COVID cases where hyperinflammatory condition is induced by SARS-CoV-2 infection. Oral anticoagulants and low-molecular-weight heparin (LMWH) may be the drugs of choice for prolonged thrombo-prophylaxis keeping in mind the predisposing risk factors like immobility, persistently elevated d-dimer levels (greater than twice the upper limit of normal) and other comorbid conditions [1].

Cardiovascular: Palpitations, dyspnea and chest pain may occur untiringly. Long-term effect of the infection include increased cardio-metabolic demand, myocardial fibrosis or scarring, arrhythmias, tachycardia and autonomic dysfunction. Cardiovascular patients should be monitored with sequential clinical, echocardiogram and electrocardiogram [1].

Neuropsychiatric: Few specific characteristic features of SARS-CoV-2 infection may include fatigue, myalgia, headache, dysautonomia, brain fog, anxiety, depression, sleep disturbances and PTSD. These could be due to inflammation, microvascular thrombosis, immune dysregulation, iatrogenic effects of medications and also psychosocial influences of the fear of infection [1].

Renal: Acute kidney infection (AKI) during acute COVID-19 appears in the majority of patients which further undergoes resolutional though decrease in eGFR has been recounted at 6 months follow-up in few cases. Such patients may benefit from early treatment and close follow-up [1].

Endocrine: Endocrine dysfunctions due to COVID-19 may involve new or deteriorating control of diabetes mellitus, subacute thyroiditis and bone demineralization [1].

Gastrointestinal and hepatobiliary: COVID-19 has the propensity to modify the GI microbiome comprising of opportunistic microorganisms and also lead to depletion of beneficial commensals that can cause deleterious effects. There can be constant shedding of fecal viral particles even after the nasopharyngeal swab test shows negative results [1].

Dermatologic: COVID-19 survivors has quite frequently complained of hair loss (approximately 20% of reported cases) [1]. Other skin manifestations of such survivors include features like acne, eczema, psoriasis, rosacea, etc. The vascular complications correlated with skin lesions can be attributed to neurogenic, microthrombotic, or immune complex mediated causes [22]. These lesions can be in the form of erythematous rashes, urticaria or hives, fluid-filled vesicles or blisters or measles-like rashes. The trunk is the most commonly affected area with mild of no itching sensation. Patients usually present with livedo reticularis which is purplish net-like discoloration of the skin occurring due to blood clotting irregularities. Hypercoagulability could manifest into lacy, dusky rashes, with dead skin cells especially on the limbs and buttocks and could also manifest into petechiae [23].

Effect on brain: Post COVID-19 patients could suffer from meningitis and encephalitis due to the viral invasion into the CNS wherein, the ACE2 receptors are present especially in the cerebral cortex and brain stem. The brain stem reflexes get suppressed and neurological indications (commonly in patients with serious diseases) may occur in combination with respiratory or other symptoms [24]. There is alteration in the oxygen and carbon dioxide saturation levels attributing to features like dizziness, headache, impaired consciousness, confusion, delirium, memory deficits, and inability to rouse [25]. Sometimes delirium can be the solitary exhibiting symptom of SARS-CoV-2infection even in younger patients. It has been documented that the occurrence of delirium in critically ill COVID-19 patients in ICU care is about 84%, amongst which two thirds display hyperactive delirium, although they received high sedation and neuroleptics for their treatment. In geriatric patients, dementia and delirium are commonly witnessed together due to SARSCoV-2 infection and it carries an increased short-term mortality rate [26]. There appears to be brain inflammation and edema due to cytokine storm and few patients exhibit sympathetic storm leading to seizure-like symptoms. Hypercoagulability and endothelial injury causes blockage of a cerebral artery leading to stroke even in younger patients with no previous history. Cerebral hemorrhage, ataxia and seizure may also be seen. Anosmia and dysgeusia (impaired sense of taste) are complained by the patients [27]. Few other features include nerve pain, weakness and pain of skeletal muscle, tingling or numbness in the limbs, rhabdomyolysis causing increased serum creatine kinase are also reported. Patients with intensive care treatment often shows encephalopathy, agitation, and confusion along with cortico-spinal tract signs with enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes [23].

Ocular effects: Ocular abnormalities chiefly comprising of conjunctivitis are mainly seen in COVID-19 patients [28]. The cells on the ocular surface act as portals of entry and reservoirs for the virus and the viral shedding is the main source of infection. The infectious virus can endure in the ocular surface for more than 3 weeks and thus, involvement of the eyes may occur during the initial stages [23].

Post covid-19 neurological syndrome: Few cases from Hongkong have shown prolonged muscle weakness and features of myopathy amongst COVID-19 survivors. Duranii., *et al.* accounted the first case of Guillain-Barre Syndrome (GBS) after COVID-19 infection but there exists a collective appreciation of a connection between COVID-19 and GBS [29]. A case of infectious acute transverse myelitis (ATM), cases of Kawasaki-like multisystem inflammatory syndromes (MIS) are also being acknowledged in children and teenagers following COVID-19 infection. Development of neurological disease specifically Alzheimer's disease has been reported to occur following COVID-19 infection. Some of the typical manifestations of post COVID-19 syndrome include persistent musculoskeletal pain, reactive arthritis, rheumatoid arthritis-like presentation (arthritis of the small joints) and femoral head necrosis. Chronic fatigue syndrome (fibromyalgia), poor sleep, tiredness, myalgia and dejection are also seen in many reported cases [17]. The correlation between COVID-19 and sensorineural hearing loss has not been thoroughly studied yet, although there exists a positive correlation between the disease and anosmia. Sensorineural hearing loss (SSNHL) is a topic which is being continuously studied on especially with regard the ideal route of steroid administration for the treatment. Hearing loss and tinnitus also can be seen in patients with COVID-19

but have not been emphasized so greatly. Sriwijitalai and Wiwanitkit in April 2020, were the ones who reported the first case of sensor neural hearing loss in a SARS-CoV-2 positive patient and since then only 4reported person this topic have been published till date. In histopathological studies, loss of hair cells and supporting cells of the organ of Corti without inflammatory cell infiltrate has been noted in patients with SSNHL, thereby, signifying that the underlying pathology of idiopathic SSNHL could be due to cellular stress pathways. SARS-CoV-2 binds to the ACE-2 receptor present on alveolar epithelial cells and endothelial cells and can also be seen in epithelial cells of the middle ear, stria vascularis and spiral ganglion in mice. Inflammatory reaction produced by SARS-CoV-2 could lead to an increase in cytokines such as TNF-α, IL 1 and IL6. A direct entry into the cochlea and inflammation causing cell stress could be correlated to persistent SSNHL in the cases of SARS-CoV-2 infection. Due to the extensive prevalence of the virus worldwide and the substantial morbidity of hearing loss, it is therefore, imperative to explore the topic further [30].

Post-intensive care syndrome (PICS): It is recognized to occur due to consistent inflammation in critically ill COVID-19 patients who recover after a prolonged ICU stay. This occurs owing to the immune-suppression and catabolism syndrome. Apart from these significant cardiovascular morbidity and mortality follow PICS, even in young patients without any known previous cardiovascular complaints [31].

Psychological effects: COVID-19 has created a huge amount of panic and psychological distress amongst the entire human population. Patients have the fear of financial difficulties and social isolation that can be seen for many days. An increase in "deaths of despair" due to substance abuse or suicide has been a matter of concern wherein the risk is greater among individuals with dementia, mental illness and autism. In such cases appropriate personal and online interaction with friends, family and support professionals seems to be advantageous. Few patients show signs of dysexecutive syndrome entailing inattention, disorientation or poorly organized movements in response to command after getting discharged from ICU. The common mental health issues like anxiety, depression and posttraumatic stress disorder (PTSD), Alzheimer's or Parkinson's disease have been seen in few patients who recover from COVID-19 [1].

Post acute covid-19 related syndromes

Multisystem inflammatory syndrome (MIS) is a distinctive characteristic of SARS-CoV-2 infection that has been recorded in literature. MIS-C was earlier portrayed in children and adolescents and was considered to occur several weeks after initial mild or asymptomatic SARS-CoV-2 infection. MIS-C is contemplated as part of the array of clinical circumstances that hypothetically follow the post-acute period. In April 2020, an inflammatory condition resembling Kawasaki disease in 8 children was reported and since then, many other such cases have been documented in literature. CDC has put forward few specific components to define MIS-C: (1) < 21 years of age with fever, laboratory findings showing inflammation and multiple organ systems affected [1]; no other alternative diagnosis thought of; and [3] molecular, serological or antigen testing (or contact with a suspected or established COVID-19 case within 4 weeks before exhibition) to substantiate SARS-CoV-2 infection [32,33].

Coronavirus disease (COVID-19) associated mucormycosis (CAM) and covid-19 associated pulmonary aspergillosis (CAPA)

Invasive mold infections (invasive pulmonary aspergillosis and pulmonary mucormycosis) share similar risk factors, clinical presentation, and radiology. Widespread use of Glucocorticoids can lead to secondary bacterial or fungal infections due to immunosuppression. Invasive pulmonary aspergillosis is common [34] however, mucormycosis (rhino-orbital mucormycosis) is uncommonly suspected or diagnosed (usually between 10 and 14 days of hospitalization).

Immune dysregulation caused by the virus and the use of concurrent immunomodulatory drugs such as Tocilizumab could further increase the risk of infections in COVID-19 patients [35]. Diabetes mellitus is the most common predisposing condition.

Pulmonary mucormycosis is increasingly diagnosed and the case fatality has improved over time [36]. Control of hyperglycemia, early treatment with liposomal amphotericin B, and surgery are essential for the successful management of mucormycosis [37].

Conclusion

The huge population of people affected by COVID-19 is unparalleled and shocking. The pandemic has disturbed the human race

financially, socially, economically, emotionally and physically. Even after recuperating from the initial COVID-19 infection, patients may present with symptoms like extreme breathlessness, fatigue, foggy brain, palpitations and memory loss. Treatment is primarily determined on reassurance, self-care and symptomatic control of the disease. However, there are presently no FDA-sanctioned treatment protocol precisely for this state. Hence, it is essential to monitor the COVID-19 survivors continuously after discharge. Therefore, it is very crucial for the healthcare officials and policymakers to make strategies in order to meet the needs of the all the people that has been affected by this pandemic. There should be appropriate global clinical registries with a conscientious system-based approach to measure, evaluate manage and report post COVID-19 patients that will assist in the investigation of the chief clinical features and effectiveness of prospective interferences of COVID-19 disease in the future.

Bibliography

1. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, Ahluwalia N, Bikdeli B, Dietz D, Der-Nigoghossian C, Liyanage-Don N, Rosner GF, Bernstein EJ, Mohan S, Beckley AA, Seres DS, Choueiri TK, Uriel N, Ausiello JC, Accili D, Freedberg DE, Baldwin M, Schwartz A, Brodie D, Garcia CK, Elkind MSV, Connors JM, Bilezikian JP, Landry DW, Wan EY. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601-615.

2. World Health Organization Website.Rolling updates on Coronavirus disease (COVID 19). (Updated on 31 March 2020).

3. Huang C, Wang Y, Li X, Ren L, Zhao J, HuY, et al. Clinical features of patientsinfected with 2019 novel coronavirus inWuhan, China. Lancet (London, England). 2020;395:497-506.

4. Mohanty A, Kabi A, Mohanty AP, Kumar N, Kumar S. Laoatory diagnosis of covid-19 infection: current issues and challenges: an Indian perspective. J Adv Med Med Res. 2020;32(14):10-17.

5. Geddes L. Why strange and debilitating coronavirus symptoms can last for months.New Scientist2020.

6. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026.

7. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382(13):1199-1207.

8. Laxminarayan R, Wahl B, Dudala SR, Gopal K, Mohan B C, Neelima S, Jawahar Reddy KS, Radhakrishnan J, Lewnard JA. Epidemiology and transmission dynamics of COVID-19 in two Indian states. Science. 2020;370(6517):691-697.

9. Padda I, Khehra N, Jafri U, Mosabbeh D, Atwal H, Musaji A, Bhullar S. Organ system effects and reinfectionof COVID-19: a review. J Res Clin Med. 2021;9:6.

10. Balachandar V, Mahalaxmi I, Subramaniam M, Kaavya J, Senthil Kumar N, Laldinmawii G, Narayanasamy A, Janardhana Kumar Reddy P, Sivaprakash P, Kanchana S, Vivekanandhan G, Cho SG. Follow-up studies in COVID-19 recovered patients - is it mandatory? Sci Total Environ. 2020;729:139021.

11. Leung NHL. Transmissibility and transmission of respiratory viruses. Nat Rev Microbiol. 2021;22:1-18.

12. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017-1032.

13. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020;581(7807):221-224.

14. Wrobel AG, Benton DJ, Xu P, et al. Author Correction: SARS-CoV-2 and bat RaTG13 spike glycoprotein structures inform on virus evolution and furin-cleavage effects. Nat Struct Mol Biol. 2020;27(10):1001.

15. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-128.

16. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol. 2018;18(2):134-147.

17. Kabi A, Mohanty A, Mohanty A, Kumar S. Post COVID-19 syndrome: a review. J Adv Med Med Res. 2020;32(24):289-295.

18. Gandhi RT, Lynch JB, Rio C. Mild or moderate COVID-19. N Engl J Med. 2010;383:1757-1766.

19. Del Rio C, Collins LF, Malani P. Long-term Health Consequences of COVID-19. JAMA. 2020.

20. Amenta EM, Spallone A, Rodriguez-Barradas MC, El Sahly HM, Atmar RL, Kulkarni PA. Postacute COVID-19: An Overview and Approach to Classification. Open Forum Infect Dis. 2020;7(12):ofaa509.

21. Katzenstein AL, Bloor CM, Leibow AA. Diffuse alveolar damage--the role ofoxygen, shock, and related factors. A review. Am J Pathol. 1976;85(1):209-228.

22. Darlenski R, Tsankov N. COVID-19 pandemic and the skin: what should dermatologists know? Clin Dermatol. 2020;38(6):785-787.

23. Jain U. Effect of COVID-19 on the Organs. Cureus. 2020;12(8):e9540.

24. Tassorelli C, Mojoli F, Baldanti F, Bruno R, Benazzo M. COVID-19: what if the brain had a role in causing the deaths? Eur J Neurol. 2020;27(9):e41-e42.

25. Wilson MP, Jack AS. Coronavirus disease 2019 (COVID-19) in neurology and neurosurgery: A scoping review of the early literature. Clin Neurol Neurosurg. 2020;193:105866.

26. De Erausquin GA, Snyder H, Carrillo M, Hosseini AA, Brugha TS, Seshadri S; CNS SARS-CoV-2 Consortium. The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. Alzheimers Dement. 2021.

27. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, Skliut M, Weinberger J, Dangayach NS, Bederson JB, Tuhrim S, Fifi JT. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med. 2020;382(20):e60.

28. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, Wu K. Characteristics of Ocular Findings of Patients with Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020;138(5):575-578.

29. Wijeratne T, Crewther S. Post-COVID 19Neurological Syndrome (PCNS); A novelsyndrome with challenges for the globalneurology community Journal of the Neurological Sciences. 2020;419:117179.

30. Koumpa FS, Forde CT, Manjaly JG Sudden irreversible hearing loss post COVID-19. BMJ Case Reports CP. 2020;13:e238419.

31. Novak P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. eNeurologicalSci. 2020;21:100276.

32. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607-1608.

33. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, Ramnarayan P, Fraisse A, Miller O, Davies P, Kucera F, Brierley J, McDougall M, Carter M, Tremoulet A, Shimizu C, Herberg J, Burns JC, Lyall H, Levin M; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2. JAMA. 2020;324(3):259-269.

34. Arastehfar A, Carvalho A, van de Veerdonk FL, Jenks JD, Koehler P, Krause R, et al. COVID-19 associated pulmonary aspergillosis (CAPA)-from immunology to treatment. J Fungi (Basel). 2020;6(2):91.

35. Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J, et al. IL-6 inhibition in critically Ill COVID-19 patients is associated with increased secondary infections. Front Med (Lausanne). 2020;7:583897.

36. Muthu V, Agarwal R, Dhooria S, Sehgal IS, Prasad KT, Aggarwal AN, et al. Has the mortality from pulmonary mucormycosis changed over time? a systematic review and meta-analysis. Clin Microbiol and Infect. 2021.

37. Deepak Garg. Valliappan Muthu. Inderpaul Singh Sehgal. Raja Ramachandran. Harsimran Kaur. Ashish Bhalla. Goverdhan D. Puri. Arunaloke Chakrabarti. Ritesh Agarwal Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. Mycopathologia. 2021;186:289-298.

Volume 5 Issue 1 January 2022