International Clinical and Medical Case Reports Journal
Review Article (ISSN: 2832-5788)

Use of Mesenchymal Stem Cells for Mitigating the Long-Term Post COVID-19 Neurological Afflictions

Diana Esquivel MS[1], Rangnath Mishra MS[1,2], Anand Srivastava MS[1,2*]

[1]Global Institute of Stem Cell Therapy and Research, Mexico, Calle 289 Alamo, Suite 5, Vicente Guerrero, 21970 Los Algodones, Baja California, USA

[2]Global Institute of Stem Cell Therapy and Research, 4660 La Jolla Village Drive, Suite 100 & 200, San Diego, California 92122, USA

Citation: *Diana Esquivel MS, Rangnath Mishra MS, Anand Srivastava MS. Use of Mesenchymal Stem Cells for Mitigating the Long-Term Post COVID-19 Neurological Afflictions. Int Clinc Med Case Rep Jour. 2023;2(18):1-11.*

Received Date: 07 November, 2023**; Accepted Date:** 06 December, 2023**; Published Date:** 10 December, 2023

[*]**Corresponding author:** Anand Srivastava, Global Institute of Stem Cell Therapy and Research, 4660 La Jolla Village Drive, Suite 100 & 200, San Diego, California 92122, USA

ABSTRACT

Ongoing studies indicate that the COVID-19 virus-induced pathobiology is still under the focus of worldwide healthcare organizations, especially because of the fact that several affected individuals continue to suffer from long-COVID-19 lingering discomforts, also known as post-COVID syndrome. Different symptoms have commonly been observed in patients even after more than 12 weeks or longer after the infection subsided. These conditions are reported to be caused by the very high production of proinflammatory cytokines, a condition known as "cytokine storm". High levels of proinflammatory cytokines can adversely affect any organ of the body including the nervous system. Distinct neurological afflictions have been reported as one of several of related-conditions to the post COVID syndrome; including acute cerebrovascular diseases, impaired cognition, memory loss, and mental health disorders. Unfortunately, there are not many clinical tools available to efficiently address symptoms related to post-covid syndrome. However, remarkable anti-inflammatory properties of mesenchymal stem cells (MSC) have been reported useful for the treatment of immune imbalance and related cases of neurological conditions, commonly found in patients with long-COVID syndrome. Although immunomodulation appears as one of the most logical mechanisms involved in the therapeutic process, more studies are needed to completely elucidate the routes involved. The established safety and therapeutic properties of the MSCs therapy make it a feasible option to treat the immune imbalance and neurological afflictions recorded in post-COVID syndrome patients. We have discussed some of the aspects involved in the light of recorded therapeutic properties of MSCs in cases of long COVID-19 syndrome.

Keywords: Mesenchymal stem cells; Neurological afflictions; Post COVID syndrome; COVID-19; Immunomodulation; Mitochondrial transference

INTRODUCTION

Even though few years have passed since the emergence of COVID-19 pandemic, ongoing research activities regarding the virus-caused pathobiology is still under the intense scrutiny of health organizations throughout the world. The disease is caused by the infection of the SARS-CoV-2 virus, a single-stranded positive-sense RNA coronavirus, with a genome size of 29,903 nucleotides; which contains 12 open reading frames, encoding 22 non-structural proteins and 4 structural proteins named envelope (E), membrane (M), nucleocapsid (N), and highly variable spike (S) proteins [1,2]. Particularly, the S protein which consists of a N-terminal S1 subunit and a C-terminal S2 subunit is crucial for the recognition process by human host cell surface receptor, the angiotensin-converting enzyme 2 (ACE2). It is the binding of the S protein of virus with the ACE2 receptor that facilitates the virus entry into the cells and then infection initiate through viral genome replication processes[2,3,4]. Although most of the virus variants are developed by nucleotide changes in the S protein, other mutation changes in proteins E, M, and N could lead to new concern-raising variants of the virus. Of special interest is the B.1.1.529 variant, also known as Omicron, which is caused by different mutations in E, M and N genes, in addition to more than thirty nucleotide changes in the S protein encoding gene [2,5,6].

Most of the patients infected with SARS-CoV-2, developed pneumonia-like symptoms including cough, fever, dysgeusia, anosmia, and myalgia [7]. However, it was noticed that even after the viral infection was under control and the host was free of the virus, a considerable number of patients could not cope with the lingering COVID 19 effects, named as long-COVID-19 syndrome, increasing the mortality rate. The long-COVID-19 effects, also known as post-COVID syndrome are the related symptoms that persist longer than 12 weeks after the infection has subsided [8]. One of the most harmful conditions observed is the excessive production of the proinflammatory cytokines, a process named as “cytokine storm”. Higher cytokine production plays important roles in immunopathology during any viral infection. However, extremely high levels of cytokines like IFN-γ, IL-1, IL-6, IL-12, and TGF-β can lead to uncontrolled immune responses as well as to a significant downregulation of antiinflammatory cytokines such as IL-10[9]. This overwhelming immune response, observed in most of the severe cases of COVID-19 infection, commonly trigger conditions like peripheral lymphopenia, high infiltration of macrophages into the lungs, contributing to acute respiratory distress syndrome; thereby, leading to general organ failure and ultimately to death[10,11]. Recent findings have pointed out the affliction of the nervous system due to the uncontrolled cytokine production, causing cellular destruction leading to a number of neurological afflictions[12,13]. Nevertheless, imbalances in cytokine production are not a unique event in COVID-19 patients. It has already been observed earlier in cases of SARS, MERS, H5N1, and H7N9 influenza infections as well as in other common respiratory infections [9].

Considering the grim of medical and social impacts of COVID-19 infections, efforts to explore different treatment options and tissue regeneration therapies were carried out globally. Of those, special interest was garnered by mesenchymal stem cells (MSCs) which demonstrated promising results due not only to immuno-modulatory activities of the stem cells to combat the cytokine storm observed during the infection, but also because of their ability to promote tissue regeneration; ultimately leading to regaining of functions of affected organs. The

extraordinary abilities of the MSCs to modulate the host's immune response has been amply demonstrated in regards to long-COVID-19 associated cytokine storm[14,15,16,17]. In addition, the regeneration of the lungs, one of the most affected organs after COVID-19 infection, promoted by MSCs further facilitate the healing process [18,19]. On the other hand, diverse studies have demonstrated that both COVID-19 and long COVID-19 can damage the nervous system up to different levels, and sometimes even cause significant morphological changes in the brain. A very interesting study demonstrated a visible reduction in the gray matter quantity and even in overall brain size, observable through magnetic resonance imaging in several patients, after COVID-19 infections [20]. Severe cases of infection have been correlated with the development of neurological disorders including acute cerebrovascular diseases, impaired cognition, loss of memory, mental health disorders and skeletal muscle injury are few of the indications. Very extensive analyses in this regard have been published by Mao et al and Xu and colleagues in 2022 [21,22]. Mitigation of the ill-effects of the cytokine storm observed in COVID-patients by MSC therapy offers a safe and promising option for treating the neurological afflictions observed in long-COVID-19 patients. This manuscript elaborates on the mechanisms of action of the MSC therapy in such patients.

Neurological disorders caused by COVID-19

COVID-19, first reported from China, is caused by SARS-CoV-2 which primarily infect ACE2 positive cells. Such cells are more commonly found in vascular linings of the blood vessels of the lungs, liver, kidney, heart, and intestines. Nevertheless, neurological disorders are also seen to frequently develop after the viral infection, because of the cytokine storm developed during the infection leading to pathological alterations [23]. Recent studies have demonstrated the expression of ACE2 receptors even in cells of tissues and organs previously considered to be not expressing the receptor, including those of the nervous system. Many animal models have been used to investigate the roles of the ACE2 receptor in the brain, and interestingly some of the findings demonstrate its participation in a number of neuropathological indications as well as in neuronal recovery from strokes, in memory formation mechanisms, and in neurogenesis [24,25,26]. While more studies are needed to fully understand how the neurological system is affected due to long-COVID-19 syndrome, distinct lines of evidence point to both direct and indirect mechanisms involved leading to tissue and organ injury. Studies have reported two possible entry routes for the SARS-CoV-2 into the central nervous system cells, which leads to the manifestation of neurological conditions. One possible suggestion is the hematogenous route, which according to postmortem observations, the virus enters the brain via the cerebral circulation. However, based on observations like the elevated incidences of olfactory disorders in COVID-19 patients, some investigators suggest retrograde axonal transport of the virus through the olfactory bulb as another potential route of entry. Overall, it is quite likely that both of the routes are at play during the infection process[27,28,29,30].

Moreover, patients diagnosed as complicated cases often in need of immediate hospitalization, have been reported to be more prone to suffer from a number of symptoms observed in post-COVID-19 syndrome. A hypercoagulable state, more commonly observed in feeble patients, could lead to the occlusion of cerebral vessels, and therefore, can lead to brain damage. In addition, the neurotoxic effects of proinflammatory cytokines have been recorded to disrupt

the integrity of the blood-brain barrier consequently leading to neurological disorders[11,21]. Based on a recent cohort study, the authors reported increased risks of development of cerebrovascular disorders including transient ischemic attacks, ischemic and hemorrhagic stroke, and cerebral venous thrombosis in patients who survived the first 30 days of COVID-19[22]. During ischemic stroke events, commonly observed in long COVID syndrome patients, the obstruction of blood flow leads to intricate pathophysiological conditions including elevation of oxidative stress, inflammation, breakdown of blood-brain barrier (BBB), calcium overload, excitotoxicity, and dysfunctional autophagy [31]. These findings are in accordance to previous reports from Wuhan in which 36.4% of 214 COVID-19 patients were reported to present with both central and peripheral neurological manifestations[21,32]. Other sensory disorders like olfactory and gustatory impairments, hearing and vision abnormalities were reported to be the most common disorders as part of post COVID-19 lingering problems[8,33]. In addition, fatigue, dizziness, memory impairment, and encephalopathy represented other high parts of the post COVID-19 syndrome related symptoms, commonly known as "brain fog". These symptoms could be lasting up to six months or even longer after the infection has been controlled and PCR tests were negative for the viral RNA[22,34].

Therapeutic properties of MSCs in neurological disorders

The remarkable abilities of the MSCs to modulate the production of cytokines, especially during autoimmune diseases which have been extensively studied, garnered a lot of attention after the COVID-19 outbreak in 2019. It has been well documented both in vitro and in vivo that MSC therapy exerts immunomodulatory effects through cell-to-cell communication as well as by paracrine activities. MSCs also have shown to exert influence onto regulatory T-cells (Treg) and monocytes, as several studies have reported changes in the polarization of the Macrophages into the M2 type of cells after interacting with the MSCs in a proinflammatory microenvironment. This process is facilitated through different soluble signaling molecules like prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), IL6 and hepatocyte growth factor (HGF) [35,36]. Similarly, it has been observed that MSCs promote the proliferation and inhibitory capabilities of Treg cells while at the same time they can inhibit activation of the T helper cells such as Th1 and Th17. In the same way, production of IL-2 and nitric oxide by the MSCs could lead to suppression of the cytotoxic T-cells to reduce cell death[37]. Overall, these processes can lead to the attenuation of the immune response, allowing the activation of regeneration signaling cascades. Presence of the inflammatory cytokines, observed in post-COVID-19 syndrome, activates MSCs in vivo to induce their immunosuppressive activities. Production of immunosuppressive molecules, including IDO and nitric oxide (NO) suppress the apoptotic effects of lymphocytes leading to an overall downregulation in the production of proinflammatory cytokines such as IL-1β, TNF-α, IFN-γ, IL-[38] . At the same time, increases in the production of anti-inflammatory mediators like IL-10, basic fibroblast growth factor (bFGF) can participate in preventing cellular death and damage to organs[38,39].

Several extensive studies focusing on the neuroprotective actions of MSCs have been carried out. Studies, both in vitro and in vivo, have confirmed the neuroprotective properties of the MSCs in a variety of indications[40,41]. A variety of studies have reported the influence of MSC administration on the promotion or downregulation of the

expression of distinct growth factors. Of special interest is the induced expression of the brain-derived neurotrophic factor (BDNF), which is known to play important roles in the neurogenesis process, including cell survival and differentiation of cells of the central nervous system (CNS); BNDF also plays significant roles in enhancing the differentiation of neural precursor cells as well as promoting the formation of synapses[42,43]. Although BDNF activates different signaling pathways, specifically the cell signaling route PI3 kinase/Akt appears to be crucial in imparting cell survival promoting effects. Besides promoting the cell-protective effects on neurons, this cell signaling pathway has been reported to be participating in survival of other types of cells like sensory neurons, cerebellar granule cells, and retinal ganglion cells[44,45,46]. Interestingly, MSC administration, which has been used as a vehicle for BDNF supplementation in treatment of an ischemic stroke model, has shown positive outcomes [47].

Furthermore, upregulation in the expression and activation of members of the Bcl-2 gene family, which act like transcription factors, has been reported to mediate endogenous neuroprotection, particularly against stroke and forebrain ischemia. Accordingly, several neuroprotective drugs also mediate activation of this gene family members with moderate results[48]. A recent study carried out the neuroprotective effects of MSC administration during ischemia events in animal models. The study results demonstrated that the MSC treated group showed significantly reduced infarct size along with reduced levels of Bcl-2 and VEGF expression. Moreover, cell viability and ATP levels were significantly increased at 6 and 24 hours after the MSC administration[49]. Similar to Bcl-2 expression, another proto-oncogene named survivin, reported to regulate the increased apoptosis-related events. Interestingly, survivin is localized with caspase 3 and 7 on microtubules within centrosomes to suppress apoptosis in cells in the G2/M phases[50]. In a synergistic manner, survivin suppresses apoptosis as Bcl-2 regulates the permeability of transition pores and release of cytochrome C during the apoptotic events. Studies have reported that intravenous administration of MSCs upregulates the anti-apoptosis factors, including survivin and Bcl-2, ultimately preventing cell deaths in ischemic brain tissues and promoting neuronal regeneration[51,52].

Similarly, remarkable ability of the MSC therapy in promotion of the angiogenesis process leading to neovascularization, has been extensively proven. Studies have recorded the mobilization and homing of MSCs into the afflicted areas to help the healing process by differentiating into the cell types of the surrounding tissue along with other healing activities mediated by their paracrine effects. Production of angiogenic growth factors like VEGF, MCP-1, and IL6 promote the differentiation and incorporation of MSCs into the ischemic tissue microenvironment. MSCs facilitate tissue regeneration by promoting new blood vessel formation thus help to increase blood supply to the affected parts of the body[53,54,55]. A number of paracrine factors are secreted by the MSCs like VEGF-A, bFGF, Ang-1, aFGF and PDGF which are known to be involved in promoting angiogenesis and tissue regeneration[56]. It has been well documented that VEGF-A induces migration of endothelial cells while promoting vessel formation which results in recruitment, retention, proliferation, migration, and differentiation of endothelial progenitor cells [57]. Recently, in vitro studies have reported that umbilical cord derived MSCs potentially promote both angiogenesis and vasculogenesis via paracrine factors, inducing the activation of the integrin β1/ ERK1/2/HIF-1α/ VEGF-A in endothelial cells[58]. Although more studies are needed to elucidate the exact cell signaling routes involved in the

promotion of angiogenesis, the production of VEGF observed after MSC administration, appears as one of the principal mechanisms involved in neovascularization.

It also has been hypothesized that the neuroprotective effects imparted by MSCs may be related to mitochondrial transfer from exogenous MSCs to damaged cells, leading to the regulation of distinct cellular functions[59]. During oxygen deprivation, which occurs in COVID-19 related ischemic conditions or in stroke events, accumulation of metabolic products like lactic acid, H+ and NADH+ is observed due to the anaerobic glycolytic metabolism switch. This leads to low levels of ATP with increases in the ROS production and eventually cell death. Furthermore, high levels of ROS could cause chronic astrogliosis impeding regeneration of several neural tissues[60,61]. Although ROS and NO have important roles in cell signaling and in neural cell communication processes, during neurological disorders as those observed after the COVID-19 infection, the excessive levels and oxidative stress results in serious damages. Detrimental effects include loss of the neuronal and glial cells, increased swelling and necrosis of organelles, lipid peroxidation, protein denaturation, and eventually increased DNA mutations[62]. MSCs transferring mitochondria during reoxygenation after deprivation of oxygen-glucose observed in neurological disorders, has been recently documented. One of the most studied proteins in regards to mitochondrial mobilization is the motor protein Miro1. This GTPase has been located on microtubules favoring and regulating the trafficking of mitochondria among cells[63]. Interestingly, up regulation of protein Miro1 has been reported after bone marrow derived-MSC administration in an ischemia animal model[49]. Similarly, in a recent investigation, MSC mitochondrial transfer to neurons were recorded after toxic oxidant exposure which was accompanied by upregulation of both Miro1 and tumor necrosis factor alpha (TNF-α) [63]. Specifically, mitochondrial mobilization has been recorded to occur via the formation of tunneling nanotubes (TNTs). TNTs are membranous channels with a diameter of 50-200nm which have an important role in delivering functional mitochondria between the plasma membranes of MSCs and adjacent host cells. This therapeutic mechanism can have significant roles in the restoration of cell functions including cellular respiration in the recipient cells, thereby, increasing ATP production and oxygen consumption[864,65]. Ultimately, this mechanism lead to restoration of cellular respiration and down regulation of ROS levels.

CONCLUSION

The cytokine storm, commonly observed in cases of COVID syndrome, can lead to neurological disorders and pose a huge socio-economic burden worldwide. Therefore, a need for new therapeutic approaches for treating them has been investigated globally. Distinct mechanisms of action involved in the therapeutic properties of MSCs, specifically in relation to immune modulation, seems to be one of the most feasible and important mechanism that appear to play crucial functions in this regard. More studies are needed to completely elucidate other cell signaling and metabolic pathways, such as angiogenesis and mitochondrial transference involved. A review on the therapeutic use of MSCs in neurological conditions has been explored by Rahman et al with promising results[66]. Clinical trials have been carried out using MSC therapy in the search for innovative and efficient treatments for neurodegenerative disorders like Parkinson's and Alzheimer's disease, in which the primary symptoms are considered to be rooted in the loss of specific neurons or neuroglia[37,67,68]. For other conditions in which neural cells are lost due to acute damage or direct trauma, such as brain strokes or traumatic brain injuries, MSC therapy has also been considered

with promising outcomes[37]. Different clinical trials related to the use of MSCs in neurological disorders are listed at https://clinicaltrials.gov/ which include neurological disorders rooted in neuro-inflammation followed by cellular and tissue damage by viral infection such as COVID-19. Though the administration routes for the best outcome have been in debate, intracranial, intravenous, and intranasal routes have been reported to be in use for the MSC therapy [69,70]. While the mechanisms of actions are still being studied, MSC therapy appears as a feasible and safe option for treating the neurological disorders related to long-COVID syndrome.

REFERENCES

1. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020;28;9(1):221-236.
2. Abavisani M, Rahimian K, Mahdavi B, Tokhanbigli S, Mollapour Siasakht M, Farhadi A, et al. Mutations in SARS-CoV-2 structural proteins: a global analysis. Virol J. 2022;18;19(1):220.
3. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;20;182(4):812-827.e19.
4. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell. 2020;3;182(5):1284-1294.e9.
5. Li S, Zhu H, Zhao M, Liu W, Wang L, Zhu B, et al. When stem cells meet COVID-19: recent advances, challenges and future perspectives. Stem Cell Res Ther. 2022;10;13(1):9.
6. Ma W, Yang J, Fu H, Su C, Yu C, et al. Genomic Perspectives on the Emerging SARS-CoV-2 Omicron Variant. Genomics Proteomics Bioinformatics. 2022;20(1):60-69.
7. Romero CNS, Colín HI, Godoy RM E, Hernández HM, et al. Clinical signs and symptoms associated with COVID19: a cross sectional study. Int. J. Odontostomat 2022;16(1):112-119.
8. Trott M, Driscoll R, Pardhan S. The prevalence of sensory changes in post-COVID syndrome: A systematic review and meta-analysis. Front. Med 2022;9:980253.
9. Liu T, Feng M, Wen Z, He Y, Lin W, Zhang M. Comparison of the Characteristics of Cytokine Storm and Immune Response Induced by SARS-CoV, MERS-CoV, and SARS-CoV-2 Infections. J Inflamm Res. 2021;23;14:5475-5487.
10. Castelli V, Cimini A and Ferri C. Cytokine Storm in COVID-19: "When You Come Out of the Storm, You Won't Be the Same Person Who Walked in". Front. Immunol 2020;11:2132.
11. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, Tarhriz V, Farjami A, Ghasemian Sorbeni F, et al. COVID-19 infection: an overview on cytokine storm and related interventions. Virol J. 2022;26;19(1):92.
12. Tutal Gursoy G, Yuksel H, Mulkem Simsek I, Oral S, Erdogan Kucukdagli F, et al. Neurological Presentations in Patients with COVID-19 in Cytokine Storm. Can J Neurol Sci. 2023;50(1):89-95.

13. Thepmankorn P, Bach J, Lasfar A, Zhao X, Souayah S, et al. Cytokine storm induced by SARS-CoV-2 infection: The spectrum of its neurological manifestations. Cytokine. 2021;138:155404.
14. Ellison-Hughes GM, Colley L, O'Brien KA, Roberts KA, Agbaedeng TA, Ross MD. The Role of MSC Therapy in Attenuating the Damaging Effects of the Cytokine Storm Induced by COVID-19 on the Heart and Cardiovascular System. Front Cardiovasc Med. 2020;7:602183.
15. Jeyaraman M, John A, Koshy S, Ranjan R, Anudeep TC, et al. Fostering mesenchymal stem cell therapy to halt cytokine storm in COVID-19. Biochim Biophys Acta Mol Basis Dis. 2021; 1;1867(2):166014.
16. Esquivel D, Mishra R, Srivastava A. Stem Cell Therapy: A Feasible Novel Therapeutic Option for COVID-19 and Long-COVID Patients. SCRT 2022;5(2):210-213.
17. Upadhyay TK, Trivedi R, Khan F, Pandey P, Sharangi AB, et al. Potential Therapeutic Role of Mesenchymal-Derived Stem Cells as an Alternative Therapy to Combat COVID-19 through Cytokines Storm. Cells 2022;11:2686.
18. Loke XY, Imran SAM, Tye GJ, Wan Kamarul Zaman WS, Nordin F. Immunomodulation and Regenerative Capacity of MSCs for Long-COVID. Int. J. Mol. Sci. 2021;22:12421.
19. Xu R, Feng Z, Wang FS. Mesenchymal stem cell treatment for COVID-19. EBioMedicine. 2022;77:103920.
20. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022;604(7907):697-707.
21. Mao L, Jin H, Wang M, Hu Y, Chen S, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-690.
22. Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. Nat Med. 2022;28(11):2406-2415.
23. Li S, Zhu H, Zhao M, Liu W, Wang L, Zhu B, et al. When stem cells meet COVID-19: recent advances, challenges and future perspectives. Stem Cell Res Ther. 2022;10;13(1):9.
24. Wang XL, Iwanami J, Min LJ, Tsukuda K, Nakaoka H, Bai HY, et al. Deficiency of angiotensin-converting enzyme 2 causes deterioration of cognitive function. NPJ Aging Mech Dis. 2016;20;2:16024.
25. Alenina N, Bader M. ACE2 in Brain Physiology and Pathophysiology: Evidence from Transgenic Animal Models. Neurochem Res. 2019;44(6):1323-1329.
26. Salamanna F, Maglio M, Landini MP, Fini M. Body Localization of ACE-2: On the Trail of the Keyhole of SARS-CoV-2. Front. Med 2020;7:594495.
27. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci. 2020;1;11(7):995-998.
28. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. CNS Neurosci Ther. 2020;26(5):499-501.

29. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020;92(7):699-702.
30. Wang Z, Yang Y, Liang X, Gao B, Liu M, Li W, et al. COVID-19 Associated Ischemic Stroke and Hemorrhagic Stroke: Incidence, Potential Pathological Mechanism, and Management. Front. Neurol 2020;11:571996.
31. He J, Liu J, Huang Y, Tang X, Xiao H, Hu Z. Oxidative Stress, Inflammation, and Autophagy: Potential Targets of Mesenchymal Stem Cells-Based Therapies in Ischemic Stroke. Front. Neurosci. 2020;15:641157.
32. Wang K, Zuo P, Liu Y, Zhang M, Zhao X, et al. Clinical and Laboratory Predictors of In-hospital Mortality in Patients With Coronavirus Disease-2019: A Cohort Study in Wuhan, China. Clin Infect Dis. 2020;71(16):2079-2088.
33. Ludwig S, Schell A, Berkemann M, Jungbauer F, Zaubitzer L, et al. Post-COVID-19 Impairment of the Senses of Smell, Taste, Hearing, and Balance. Viruses 2022;14:849.
34. Altuna M, Sánchez-Saudinós MB, Lleó A. Cognitive symptoms after COVID-19. Neurology Perspectives. 2021;1:S16–24.
35. Song N, Scholtemeijer M, Shah K. Mesenchymal Stem Cell Immunomodulation: Mechanisms and Therapeutic Potential. Trends Pharmacol Sci. 2020;41(9):653-664.
36. Müller L, Tunger A, Wobus M, von Bonin M, Towers R, et al. Immunomodulatory Properties of Mesenchymal Stromal Cells: An Update. Front. Cell Dev. Biol. 2020;9:637725.
37. Isaković J, Šerer K, Barišić B, Mitrečić D. Mesenchymal stem cell therapy for neurological disorders: The light or the dark side of the force? Front. Bioeng. Biotechnol. 2023;11:1139359.
38. Wang L, Li Y, Xu M, Deng Z, Zhao Y, et al. Regulation of Inflammatory Cytokine Storms by Mesenchymal Stem Cells. Front. Immunol. 2021;12:726909.
39. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-613.
40. Zhang Y, Yu S, Tuazon JP, Lee JY, Corey S, Kvederis L, et al. Neuroprotective effects of human bone marrow mesenchymal stem cells against cerebral ischemia are mediated in part by an anti-apoptotic mechanism. Neural Regen Res 2019;14(4):597-604.
41. Osborne A, Sanderson J, Martin KR. Neuroprotective Effects of Human Mesenchymal Stem Cells and Platelet-Derived Growth Factor on Human Retinal Ganglion Cells. Stem Cells. 2018;36(1):65-78.
42. Ghasemi M, Roshandel E, Mohammadian M, Farhadihosseinabadi B, Akbarzadehlaleh P, Shamsasenjan K. Mesenchymal stromal cell-derived secretome-based therapy for neurodegenerative diseases: overview of clinical trials. Stem Cell Res Ther. 2023;14(1):122.
43. Kim HJ, Lee JH, Kim SH. Therapeutic effects of human mesenchymal stem cells on traumatic brain injury in rats: secretion of neurotrophic factors and inhibition of apoptosis. J Neurotrauma. 2010;27(1):131-138.

44. Kaplan DR, Miller FD. Neurotrophin signal transduction in the nervous system. Curr Opin Neurobiol. 2000;10(3):381-391.
45. Yamada M, Tanabe K, Wada K, Shimoke K, Ishikawa Y, Ikeuchi T, et al. Differences in survival-promoting effects and intracellular signaling properties of BDNF and IGF-1 in cultured cerebral cortical neurons. J Neurochem. 2001;78(5):940-51.
46. Wilkins A, Kemp K, Ginty M, Hares K, Mallam E, Scolding N. Human bone marrow-derived mesenchymal stem cells secrete brain-derived neurotrophic factor which promotes neuronal survival in vitro. Stem Cell Res. 2009;3(1):63-70.
47. Jeong CH, Kim SM, Lim JY, Ryu CH, Jun JA, Jeun SS. Mesenchymal stem cells expressing brain-derived neurotrophic factor enhance endogenous neurogenesis in an ischemic stroke model. Biomed Res Int. 2014;2014:129145.
48. Wu C, Fujihara H, Yao J, Qi S, Li H, Shimoji K, Baba H. Different expression patterns of Bcl-2, Bcl-xl, and Bax proteins after sublethal forebrain ischemia in C57Black/Crj6 mouse striatum. Stroke. 2003;34(7):1803-1808.
49. Wei W, Wu D, Duan Y, Elkin KB, Chandra A, Guan L, et al. Neuroprotection by mesenchymal stem cell (MSC) administration is enhanced by local cooling infusion (LCI) in ischemia. Brain Res. 2019;1724:146406.
50. Shin S, Sung BJ, Cho YS, Kim HJ, Ha NC, et al. An anti-apoptotic protein human survivin is a direct inhibitor of caspase-3 and -7. Biochemistry. 2001;40(4):1117-1123.
51. Okazaki T, Magaki T, Takeda M, Kajiwara Y, Hanaya R, Sugiyama K, et al. Intravenous administration of bone marrow stromal cells increases survivin and Bcl-2 protein expression and improves sensorimotor function following ischemia in rats. Neurosci Lett. 2008;430(2):109-114.
52. Pavlyukov MS, Antipova NV, Balashova MV, Vinogradova TV, Kopantzev EP, Shakhparonov MI. Survivin monomer plays an essential role in apoptosis regulation. J Biol Chem. 2011;1;286(26):23296-307.
53. Kwon HM, Hur SM, Park KY, Kim CK, Kim YM, et al. Multiple paracrine factors secreted by mesenchymal stem cells contribute to angiogenesis. Vascul Pharmacol. 2014;63(1):19-28.
54. Tao H, Han Z, Han ZC, Li Z. Proangiogenic Features of Mesenchymal Stem Cells and Their Therapeutic Applications. Stem Cells Int. 2016;2016:1314709.
55. Andrzejewska A, Dabrowska S, Lukomska B, Janowski M. Mesenchymal Stem Cells for Neurological Disorders. Adv Sci (Weinh). 2021;8(7):2002944.
56. Edwards SS, Zavala G, Prieto CP, Elliott M, Martínez S, et al. Functional analysis reveals angiogenic potential of human mesenchymal stem cells from Wharton's jelly in dermal regeneration. Angiogenesis. 2014;17(4):851-866.
57. Grunewald M, Avraham I, Dor Y, Bachar-Lustig E, Itin A, Jung S, et al. VEGF-induced adult neovascularization: recruitment, retention, and role of accessory cells. Cell. 2006;124(1):175-89.

58. Wu M, Chen L, Qi Y, Ci H, Mou S, et al. Human umbilical cord mesenchymal stem cell promotes angiogenesis via integrin β1/ERK1/2/HIF-1α/VEGF-A signaling pathway for off-the-shelf breast tissue engineering. Stem Cell Res Ther. 2022;13(1):99.
59. Liu K, Guo L, Zhou Z, Pan M, Yan C. Mesenchymal stem cells transfer mitochondria into cerebral microvasculature and promote recovery from ischemic stroke. Microvasc Res. 2019;123:74-80.
60. Han D, Zheng X, Wang X, Jin T, Cui L, Chen Z. Mesenchymal Stem/Stromal Cell-Mediated Mitochondrial Transfer and the Therapeutic Potential in Treatment of Neurological Diseases. Stem Cells Int. 2020;2020: 8838046.
61. Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. Trends Neurosci. 2009;32(12):638-647.
62. Zhao J. Interplay among nitric oxide and reactive oxygen species: a complex network determining cell survival or death. Plant Signal Behav. 2007;2(6):544-547.
63. Tseng N, Lambie SC, Huynh CQ, Sanford B, Patel M, et al. Mitochondrial transfer from mesenchymal stem cells improves neuronal metabolism after oxidant injury in vitro: The role of Miro1. J Cereb Blood Flow Metab. 2021;41(4):761-770.
64. Nair S, Rocha-Ferreira E, Fleiss B, Nijboer CH, Gressens P, Mallard C, et al. Neuroprotection offered by mesenchymal stem cells in perinatal brain injury: Role of mitochondria, inflammation, and reactive oxygen species. J Neurochem. 2021;158(1):59-73.
65. Caicedo A, Fritz V, Brondello JM, Ayala M, Dennemont I, et al. MitoCeption as a new tool to assess the effects of mesenchymal stem/stromal cell mitochondria on cancer cell metabolism and function. Sci Rep. 2015;5:9073.
66. Rahman MM, Islam MR, Islam MT, Harun-Or-Rashid M, Islam M, et al. Stem Cell Transplantation Therapy and Neurological Disorders: Current Status and Future Perspectives. Biology 2022;11:147.
67. Hernández AE, García E. Mesenchymal Stem Cell Therapy for Alzheimer's Disease. Stem Cells Int. 2021;2021:7834421.
68. Heris RM, Shirvaliloo M, Abbaspour-Aghdam S. et al. The potential use of mesenchymal stem cells and their exosomes in Parkinson's disease treatment. Stem Cell Res Ther 2022;13:371.
69. Das M, Mayilsamy K, Mohapatra SS, Mohapatra S. Mesenchymal stem cell therapy for the treatment of traumatic brain injury: progress and prospects. Rev Neurosci. 2019;30(8):839-855.
70. Zhang Y, Dong N, Hong H, Qi J, Zhang S, et al. Mesenchymal Stem Cells: Therapeutic Mechanisms for Stroke. Int. J. Mol. Sci. 2022;23:550.