



REVIEW

# Potential for Stem Cell-Based Therapy in the Road of Treatment for Neurological Disorders Secondary to COVID-19

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Received: 28 January 2021 / Revised: 19 September 2021 / Accepted: 1 October 2021 / Published online: 29 October 2021  
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## Abstract

The severe acute respiratory syndrome coronavirus 2 has led to the worldwide pandemic named coronavirus disease 2019 (COVID-19). It has caused a significant increase in the number of cases and mortalities since its first diagnosis in December 2019. Although COVID-19 primarily affects the respiratory system, neurological involvement of the central and peripheral nervous system has been also reported. Herein, the higher risk of neurodegenerative diseases in COVID-19 patients in future is also imaginable. Neurological complications of COVID-19 infection are more commonly seen in severely ill individuals; but, earlier diagnosis and treatment can lead to better long-lasting results. In this respect, stem cell biotechnologies with considerable self-renewal and differentiation capacities have experienced great progress in the field of neurological disorders whether in finding out their underlying processes or proving them promising therapeutic approaches. Herein, many neurological disorders have been found to benefit from stem cell medicine strategies. Accordingly, in the present review, the authors are trying to discuss stem cell-based biotechnologies as promising therapeutic options for neurological disorders secondary to COVID-19 infection through reviewing neurological manifestations of COVID-19 and current stem cell-based biotechnologies for neurological disorders.

**Lay Summary** Due to the substantial burden of neurological disorders in the health, economic, and social system of society, the emergence of neurological manifestations following COVID-19 (as a life-threatening pandemic) creates the need to use efficient and modern methods of treatment. Since stem cell-based methods have been efficient for a large number of neurological diseases, it seems that the use of mentioned methods is also effective in the process of improving neurological disorders caused by COVID-19. Hereupon, the current review aims to address stem cell-based approaches as treatments showing promise to neurological disorders related to COVID-19.

**Keywords** COVID-19 · Neurologic manifestations · Nervous system diseases · SARS-CoV-2 · Stem cells · Stem cell research

## Abbreviations

COVID-19	Coronavirus disease 2019	ACE2	Angiotensin converting enzyme 2
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2	PPI	Protein-protein interaction
CT scan	Computed tomography scan	TMPRSS2	Transmembrane serine protease 2
RT-PCR	Real-time polymerase chain reaction	IFN- $\gamma$	Interferon gamma
		Th1	T-helper1
		IL	Interleukin
		TNF	Tumor necrosis factor
		ARDS	Acute respiratory distress syndrome
		CRP	C-reactive protein
		CNS	Central nervous system
		PNS	Peripheral nervous system
		BBB	Blood-brain barrier
		ADEM	Acute disseminated encephalomyelitis
		GBS	Guillain-Barre syndrome
		ADR	Adverse drug reactions

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CQ	Chloroquine
HCQ	Hydroxychloroquine
iPSC	Induced pluripotent stem cells
ESC	Embryonic stem cells
DA	Dopamine
GABA	Gamma-aminobutyric acid
MSCs	Mesenchymal stem cells
NSCs	Neural stem cells
BDNF	Brain-derived neurotrophic factor
VEGF	Vascular endothelial growth factor
NGF	Nerve growth factor
MS	Multiple sclerosis
ALS	Amyotrophic lateral sclerosis
CDNF	Cerebral dopamine neurotrophic factor
GDNF	Glial-derived neurotrophic factor
NPs	Neural progenitors
HSC	Hematopoietic stem cell
NCSC	Neural crest stem cells
DPSC	Human dental pulp stem cells
EPI-NCSC	Epidermal neural crest stem cells
iNSCs	Induced neural stem cells

## Introduction

Nowadays, there is a current global outbreak of coronavirus disease 2019 (COVID-19) resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or a novel type known member of  $\beta$  coronaviruses [13, 15, 16, 113]. Until now, the most common early manifestations of COVID-19 appear to occur in the respiratory system. But there are ample shreds of evidence that it can be spread to other major organs, including the central and peripheral nervous systems (CNS and PNS). In this context, based on the variation in the severity of symptoms in the affected area, the subsequent destructive health, economic, and social burdens are also different. Hence, in many cases in addition to the need for costly treatments, it can lead to irreversible complications and death [134, 145, 148]. Since finding effective treatment options to reduce the destructive consequences of the disease is always an important goal of health systems [97], this is also very important for the reduction of COVID-19 manifestations in various organs, especially the nervous system. Herein, cell therapy and regenerative medicine investigations as a pivotal part of clinical investigations promise powerful developments in medical science [13–15, 44–47, 102, 106–108, 115]. In this respect, the emphasis of many studies is related to the safety and efficacy of the stem cell therapies for treating neurological disorders. Mentioned therapies rely on various factors, including the form and seriousness of the disorders, medical comorbidities, and other specific dilemmas [7, 32, 40, 42, 43, 45, 47, 68–70, 85, 105–108, 126]. Overall, given the issues raised, the purpose

of writing the present review is to consider studies on the impacts of stem cells to improve neurological manifestations following COVID-19.

## COVID-19 Infection

COVID-19 infection caused by SARS-CoV-2 is a recent public health challenge spread around the world. SARS-CoV-2 originated from bats, transmitted to humans by the means of intermediate animals, and thus affecting the global medical, economic, and public health. The incubation period of the disease ranges from 2 to 14 days [122, 125], and respiratory droplets, direct contacts, and contaminated surfaces are mentioned to be the three ways of transmission [86]. The disease can be diagnosed by computed tomography scan (CT scan), real-time-polymerase-chain-reaction (RT-PCR), antibody detection (with lower sensitivity), and viral culture (a more time-consuming method) [91]. COVID-19 typically results in respiratory and enteric infection. However, age, hypertension, diabetes mellitus, and chronic lung disease are some factors that can lead to worse outcomes [101].

## Mechanism of Action

Studies have shown that SARS-CoV-2 utilizes angiotensin-converting-enzyme 2 (ACE2) as a cellular receptor for entry into the human cells. ACE2 presents in different tissues and organs including alveolar epithelial cells as well as renal, cardiovascular, and gastrointestinal tissues [6]. Moreover, it has been found that the ACE2 receptor utilized by SARS-CoV acts as a mediator of neuronal damage due to the coronavirus infection. It may indicate the probable similar neurovirulence for SARS-CoV-2, too [6]. Also, protein–protein interaction (PPI) and recognized hub genes have effects on the viral activity and cytokine secretion [6]. Cellular entry of coronavirus consists of receptor binding and virus-cell fusion following proteolysis. After receptor binding, transmembrane-serine-protease 2 (TMPRSS2) as proximal serine proteases takes part in spike (s) protein priming of SARS-CoV-2 and spike cleaving. Thereafter, the spike fusion peptide releases by proteases like Furin following viral entry through the endosomal pathway. In this regard, the low pH and also proteases may help SARS-CoV-2 reach the cytosol. It may lead to the mature virion production and more spread due to more viral replication [87]. In the next step, activation of pro-inflammatory cytokines results in the apoptosis and necrosis of infected cells along with triggering inflammatory responses. Producing interferon-gamma (IFN- $\gamma$ ) by CD4+ T-helper1 (Th1) cells to provide immunity and recruitment of neutrophils and macrophage by Th17 cells to produce interleukin (IL)-17, IL-21, and IL-22 are also in the next parts of infection [31]. Indeed, inflammation has an

important role in executing proper immune responses and it is required to eliminate infection successfully. However, SARS-CoV-2 infection results in excessive and prolonged inflammatory responses in some patients named cytokine storm. Hereupon, cytokine storm is defined as the sudden and acute production of different pro-inflammatory cytokines such as interferon, IL-6, IL-1, and tumor necrosis factor (TNF)- $\alpha$  that may lead to more severe complications and multiple organ dysfunction [30, 104, 114, 123, 147]. Cytokine storm has a mentionable connection to a potential neurological injury mechanism [6]. Moreover, acute respiratory distress syndrome (ARDS) followed by lower oxygen saturation is mentioned to be the main cause of death among infected patients with SARS-CoV-2 in which this higher production of inflammatory responses has an important effect [2, 104].

### Symptoms, Signs, and Complications

COVID-19 can be associated with a different range of symptoms from asymptomatic to severe respiratory failure [27]. Nevertheless, fever, cough, shortness of breath, muscle ache, confusion, and headache are more common symptoms of disease [27, 144]. Gastrointestinal involvement can be also found with the presentation of diarrhea, nausea, and vomiting [101]. On the other hand, CT scan imaging has shown bilateral involvement, especially with the characteristic of multiple lobular ground-glass opacities in infected patients. Thus, asymmetric ground-glass opacities and absent pleural effusions are mentionable clinical features which can be found on radiographs of symptomatic patients [27, 39, 104, 154]. Laboratory findings among patients hospitalized with pneumonia due to COVID-19 on their admission indicate the presence of leucocytosis (24–30%), leucopenia (9–25%), and lymphopenia (63%). Higher ranges of alanine aminotransferase/aspartate aminotransferase were also seen among laboratory abnormalities (37%) [150, 153]. Mild thrombocytopenia, a higher level of lactate dehydrogenase C-reactive protein (CRP), and lower pro-calcitonin levels have been also reported [54, 101]. Patients with the requirement of intensive treatment unit have shown higher prothrombin and D-dimer levels, too (Fig. 1). Herein, increased troponin levels found in patients can be suggestive of virus-associated myocarditis. D-dimer levels are mentioned to be considered indicators for coagulopathy which is related to the higher mortality rate from coronavirus infection [12]. As it was mentioned, COVID-19 infection can lead to the multiple organ dysfunction and cause complications in different organs such as the respiratory system (through pneumonia following by ARDS) and cardiovascular system (which can be manifested by arrhythmia, cardiac inflammation, myocardial infarction, and thrombosis). The involvement of the gastrointestinal system (by anorexia, nausea, vomiting) and

urinary system (for instance, renal impairment) has been also stated about the complications of COVID-19. Septic shock, miscarriage, and premature delivery are also other complications [9]. Thus, the effects of coronaviruses are not limited to the respiratory tract. In this regard, they can also invade the nervous system leading to the neurological abnormalities [25].

### Neurological Events Secondary to COVID-19

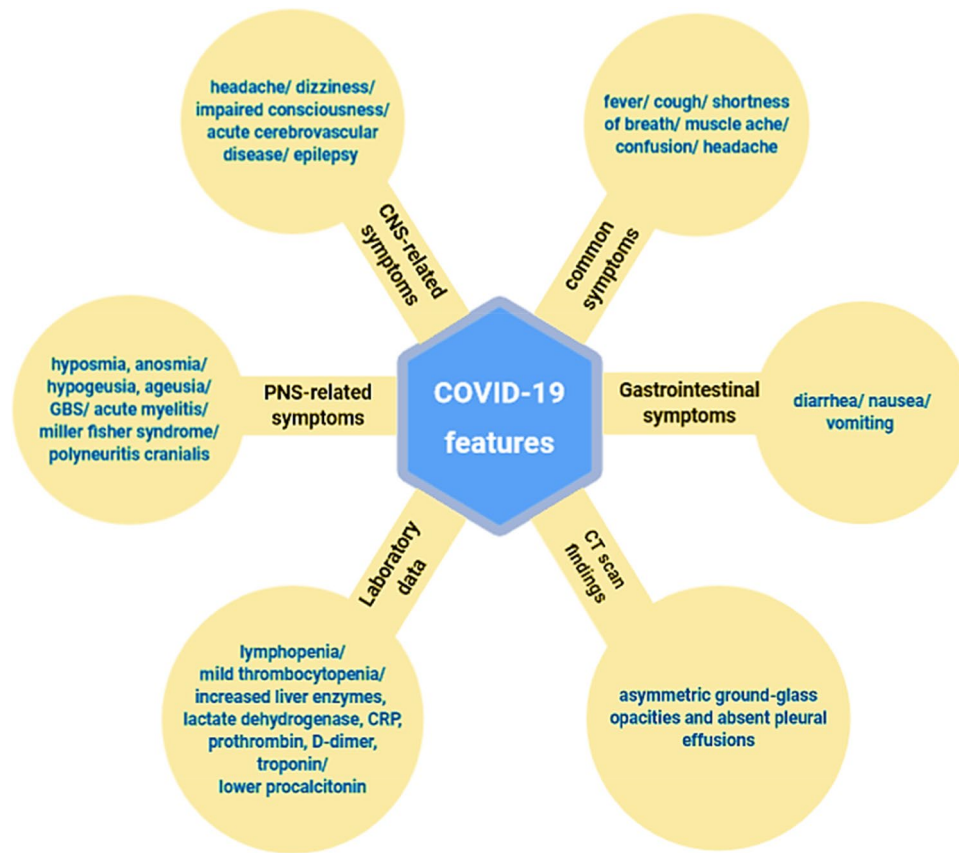
Although COVID-19 is primarily introduced as a respiratory disease, its effects on the other organs like nervous system (on both CNS and PNS) and its extrapulmonary features are well established, too [6, 98]. Indeed, the brain is a potential target for SARS-CoV-2 because of ACE2 expression in both neurons and glial cells [60]. ACE2 receptors are mainly found in the brainstem (in the responsible regions for the regulation of cardiovascular function). In addition to utilizing these receptors, a direct trans-synaptic route using the olfactory bulb (by inhalation) is another possible way of invasion [130]. The blood circulatory pathway, followed by cytokine release, and increasing the permeability of blood–brain barrier (BBB) are also other probable routes for the virus to infect CNS [145]. Thus, reactivating astrogliosis and activation of microglia due to the viral invasion can lead to the considerable neuro-inflammatory cascade. Moreover, the BBB may be compromised because of the systemic inflammation related to COVID-19 infection. It may result in disturbed brain homeostasis and death of neural cells. Chemosensory neural cells (related to respiratory and cardiovascular regulation) and neurons of the respiratory center can be also affected in this infection pathway [121, 130]. Therefore, the massive neurologic effects and complications of COVID-19 related to the viral infection, immune response, and critical illness have been explained. The complications related to the therapies and recovery managements are also found as the COVID-19 neurologic effects [6].

### Neurological Manifestations of COVID-19

Neurotoxicity due to direct, indirect, and post-infectious effects of COVID-19 should be considered fundamentally to provide more effective management approaches for patients [60]. Taken together, autoimmune processes, thrombotic events, BBB alterations, and cytokine-related disturbances may lead to both PNS and CNS manifestations (Fig. 1) [133].

### CNS-Related Effects

Hyposmia/anosmia, hypogeusia/ageusia, headache, dizziness, impaired consciousness in addition to acute cerebrovascular disease, and epilepsy can be mentioned as some



**Fig. 1** Some features of COVID-19. Fever, cough, shortness of breath, muscle ache, confusion, and headache are more common symptoms of the disease [27], Wolff, Nee et al. 2020). Gastrointestinal involvement including the presence of diarrhea, nausea, and vomiting can be also associated with COVID-19 [101]. Hyposmia/anosmia, hypogeusia/ageusia, GBS, acute myelitis, Miller Fisher syndrome, and polyneuritis cranialis are some PNS-related effects of COVID-19 [93, 94, 121], whereas headache, dizziness, impaired consciousness, acute cerebrovascular disease, and epilepsy are CNS-related manifestations [93, 94, 103], Wu, Xu et al. 2020).

Asymmetric ground-glass opacities and absent pleural effusions are mentionable clinical features which can be seen on radiographs of symptomatic patients (Ragab, Salah Eldin et al. 2020). Lymphopenia, mild thrombocytopenia in addition to the increased liver enzymes, lactate dehydrogenase, CRP, prothrombin, D-dimer, and troponin levels and also lower levels of procalcitonin can be found on laboratory data [12, 54, 150, 153]. COVID-19, coronavirus disease 2019; GBS, Guillain–Barre syndrome; PNS, peripheral nervous system; CNS, central nervous system; CT scan, computed tomography scan; CRP, C-reactive protein

of the CNS-related effects of COVID-19 infection [93, 94, 103, 145]. Anosmia with or without dysgeusia is a frequent symptom among COVID-19 patients [26, 65, 110]. It is mostly reported found in the early 20 s of patients and otherwise healthy/asymptomatic patients [8]. It has been found that anosmia/hyposmia can be the only symptom of the disease especially in paucisymptomatic patients [67]. Ageusia is also reported to be found mostly in the initial presentation of the disease and in asymptomatic individuals [35, 93, 94]. Damaging the olfactory receptor nerves because of viral replication (in the olfactory cells) can lead to anosmia. Indeed, replication of SARS-CoV-2 in the non-neural olfactory cells can lead to the damages of olfactory receptor nerves, and subsequently, anosmia occurs [146]. Headache can be mentioned as a common symptom of COVID-19 presenting in up to 40% of infected individuals [19, 33].

Although the probable role of direct viral invasion in nervous system involvement and cytokine storm syndrome has been found, there is limited information about the headache mechanisms and timing in COVID-19 patients [21]. However, according to a cross-sectional study, it has been found that headache due to COVID-19 is mostly moderate to severe with pressing and diffuse characteristics. Also, COVID-19-related headaches have shown a relation to the past medical history of primary headache events, comorbidities, or dehydration [81]. Dizziness is another important symptom of the disease that can occur as the result of hypoxia and hyper-coagulopathy in addition to the direct invasion and immune-mediated processes. Although dizziness is mentioned to be a nonspecific COVID-19 symptom, it requires notable attention to find out its leading cause such as vestibular neuritis, acute otitis media, or stroke [119]. It

has been reported that impaired consciousness with different manifestations (including somnolence, confusion, delirium, stupor, and even coma) has been observed in almost 15% of hospitalized COVID-19 patients. In addition to the direct effects of the virus, some other factors including pain, prolonged hospitalization, metabolic conditions, and constipation can affect this condition. Pro-inflammatory cytokine release along with tissue hypoxia, sleep deprivation, and neurotransmitter imbalance are explained as the contributing underlying pathways [151]. Herein, delirium can be introduced as a marker for severe conditions of COVID-19, especially in older individuals with a preexisting history of neuropsychiatric comorbidity [136]. Delirium along with other neurological manifestations should be regarded seriously because they can lead to sustained sedation, mechanical ventilation, and thus worse prognosis [50]. On the other hand, disruption of BBB, impairments of ion channel functions, alterations in glutamate, aspartate, and  $\gamma$ -aminobutyric acid levels along with increased cytokine production can lead to epilepsy and seizures [95]. According to the related studies, recurrent transient seizures may be found even in patients without a history of epileptic seizures or a family history of it which demonstrates the importance of physicians' awareness about it [93, 94]. However, minimal risk is imagined for seizures in the acute stage of the disease [80]. Cerebrovascular diseases are also other neurological manifestations that can be provoked by COVID-19 as a viral infection. In this regard, downregulated natural anti-coagulant processes because of inflammatory mediators and coagulation system disturbances can lead to cerebrovascular diseases [93, 94]. Higher D-dimer levels and severe platelet reduction which are often seen in critically ill patients can show their tendency to cerebrovascular events [145]. Thus, COVID-19 hyper-coagulopathy (which can be mentioned as sepsis-induced coagulopathy) may predispose patients to stroke [52]. In addition to these more common neurological signs and symptoms explained, ataxia, viral encephalitis, acute disseminated encephalomyelitis (ADEM), meningitis, encephalitis, endotheliitis, and neurodegenerative diseases are also other important neurological manifestations of COVID-19 according to the CNS involvement [4, 8, 22, 93, 94]. Different manners in which COVID-19 affects the brain and causes nervous tissue damages (like direct infection, infection of the olfactory bulb neuron, severe systemic inflammation, global brain ischemia, increased intravascular clotting, and psychological stress) may lead to the increased risk of neurodegenerative diseases and induced dementia [82, 124, 137].

### PNS-Related Effects

PNS-related effects of COVID-19 infection are usually less severe, such as Guillain–Barre syndrome (GBS), acute

myelitis, Miller Fisher syndrome, and polyneuritis cranialis [93, 94, 121]. GBS as a heterogeneous disorder related to the viral infection is another PNS-related manifestation which can be linked to the COVID-19 infection and mostly seen in elderly men [109]. Although the exact cause of the existing relationship between SARS-CoV-2 infection and GBS is not clear yet, autoimmune processes according to COVID-19 through pathogenic priming can have an important role [133]. It has been found that GBS due to SARS-CoV-2 infection has the most characteristics of classic GBS (post-infectious) and it is probably related to the same immune-mediated pathogenetic pathways [3].

### Psychological and Cognitive Disorders

Previous investigations proposed at evaluating the psychological symptoms of epidemics and pandemics have shown that restrictive measures including quarantine and social/physical distancing can affect people's psychological health. Nowadays, clinicians have detected a surge in some people especially children suffering from including anorexia nervosa, bulimia nervosa, binge eating disorder, and other eating disorders (EDs) as a result of the COVID-19 epidemic. However, there is no epidemiological evidence to illustrate how eating disorder rates changed during the pandemic. Herein, environmental measures to prevent the spread of the COVID-19 have an impact on food availability and access to appropriate coping techniques, as well as contributing to weight-phobic media messaging that may be especially harmful to individuals with EDs. Moreover, changes in socialization and routine, stress, and trauma experiences that are occurring around the world may all be detrimental to ED risk and recovery. On the other hand, one neurological symptom that COVID-19 individuals typically experience is lingering mental fog or cognitive impairment. Mental fog can remain for months after the sickness has passed in certain circumstances. In general, mental fog can be caused by a lack of sleep, excessive work, or stress. Of course, the cause of mental fog in patients who have COVID-19 may be caused by inflammation in and around the brain. Additionally, physiological and psychological aspects are thought to be involved, but generally are still under investigation by researchers. Trouble sleeping, insomnia, headaches, low energy or fatigue, impaired cognitive function, mood swings, irritability, forgetfulness trouble concentrating, low motivation, lack of ideas, and mild depression are some of the mental fog symptoms.

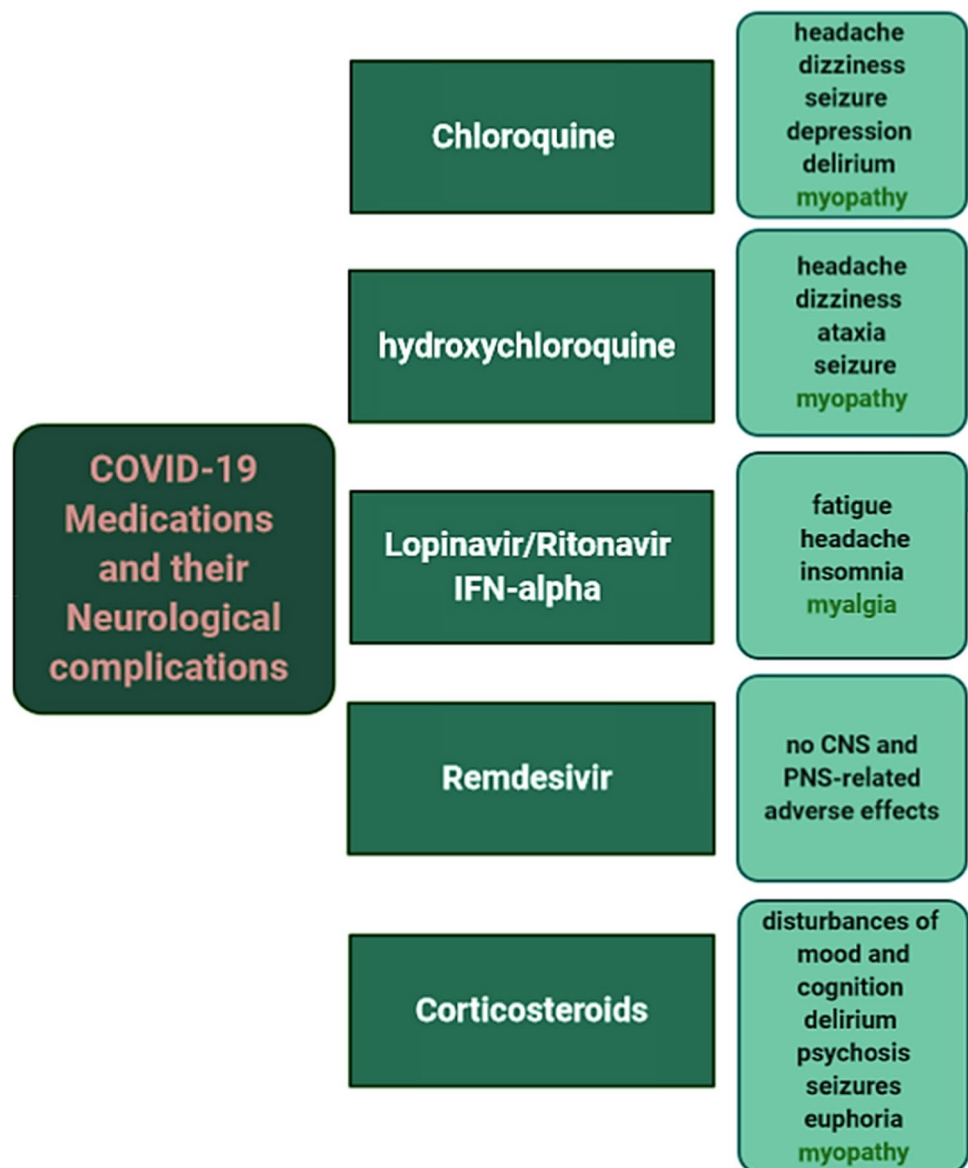
### Neurological Complications of COVID-19 Medications

Besides the neurologic manifestations stated about COVID-19 infection, there are many neurologic adverse

drug reactions (ADRs) and drugs' pharmacokinetics associated with routine medications used for COVID-19 (Fig. 2) [37]. Chloroquine and hydroxychloroquine (CQ/HCQ) treatment for COVID-19 consists of several neurological adverse effects. In this regard, CQ has been reported to have headache, dizziness, and seizures [36], in addition to depression and delirium as some CNS-related adverse effects [96]. Also, headache, dizziness [37], ataxia, and seizure are some adverse effects of HCQ related to the CNS involvement [36]. Both CQ and HCQ may lead to myopathy as their PNS-related adverse effects [1, 55]. Myalgia is a PNS-related effect of both lopinavir/ritonavir and IFN-alpha that can cause fatigue, headache, and insomnia as their CNS-related reactions

[37]. Remdesivir can be also another promising drug for COVID-19 management. However, more evaluations are required to indicate its effectiveness along with its adverse events and safety, and it typically shows low quality of adverse events [66]. In this regard, according to the studies, no CNS- and PNS-related adverse effects have been found for it yet. Corticosteroids are introduced as another class of drugs that can be used in COVID-19 management. Myopathy and neuropathy [37], as well as disturbances of mood, cognition, sleep, delirium, and psychosis, are some possible adverse effects of them [140]. Changing intracellular potassium metabolism and brain sodium levels can be a cause for the adverse effects of corticosteroids leading to seizures, psychosis, sleep disturbances, euphoria, and mental abnormalities [29].

**Fig. 2** Neurological complications of COVID-19 medications. Some of the drugs used during COVID-19 management are chloroquine (with headache, dizziness, seizure, depression, and delirium as some CNS-related adverse effects and myopathy as its PNS-related adverse effect), hydroxychloroquine (with the same PNS adverse effect and headache, dizziness, ataxia, and seizure as some CNS-related adverse reactions), lopinavir/ritonavir and IFN-alpha (with fatigue, headache, and insomnia as some CNS-related adverse effects and myalgia as PNS-related adverse reaction), remdesivir (with no known CNS- and PNS-related adverse effects), and corticosteroids (with CNS-related adverse effects of mood/cognition disturbances, delirium, psychosis, seizures, and euphoria along with myopathy as PNS-related adverse effect) [1, 36, 37, 55, 66, 96, 140]. COVID-19, coronavirus disease 2019



## Brief Review of Stem Cell Medicine

Stem cells can be divided into the groups of totipotent, pluripotent, multipotent, and unipotent stem cells. Totipotent stem cells can generate all types of developing organism's cells and differentiate into embryonic and extraembryonic tissues. Pluripotent stem cell as descendants of these cells can produce all differentiated cells of the body [23, 53]. The next main type of stem cells, multipotent stem cells, also have the ability to generate a number of types, but especially those from a related family [91]. Moreover, unipotent stem cells can create cells of their own type along a solitary lineage. In general, stem cells with their capacity of self-renewal and differentiation into different kinds of cells (such as blood, heart, cartilage, and nervous cells) have become an interesting part of treatment strategies for several disorders. Various sources including embryonic, adult, fetal, and induced pluripotent stem cells (iPSC) have been known for this kind of therapy [44, 46, 100, 106–108, 120]. Indeed, the field of stem cell therapy and regenerative medicine has experienced significant progress due to the higher demands for the new therapeutic strategies. It made stem cell-based therapies a promising and important therapeutic approach for chronic and long-lasting disorders [5, 38, 41–43]. Some of the disorders which may benefit from stem cell medicine are recurrent cancers, age-related functional defects, immune system, and blood disorders, heart failure, and diabetes as well as disorders related to the skin, lung, eye, muscles, and digestive system [84]. Stem cell therapies are also considered to be a promising approach to attenuate inflammatory processes of COVID-19 [28, 74, 100, 116]. Neurological disorders (consisting of CNS and PNS-related disorders) mostly have limited therapeutic options and poor drug approval rates. In this context, stem cell-based therapy has also provided hopes for patients suffering from neurological disorders [10, 11].

### Stem Cell-Based Biotechnologies for Neurological Disorders

Human embryonic stem cells (ESCs) as undifferentiated pluripotent cell lines with specific embryonic antigens can be reached from the blastocyst. They have a significant ability for differentiation into all three germ lineages including nervous tissue [34, 51, 58, 118]. Some transcription factors and other features of ESCs that make them proper cell sources for therapy of neurological disorders include their capacity for generating neurons and glia following transplantation as well as their ability for integration into the local structure because of their long-lasting

stability. They can also provide trophic support by secreting neurotrophic factors [127]. Despite the known capacity of human ESCs as a source of defined cells in regenerative medicine, there are also some ethical concerns about scientific researches on human blastocysts. The probable neoplastic potential of ESCs also has provided some challenges [20, 58]. On the other hand, iPSCs with their clear pluripotency potential can be effective for rejection-tolerance personalized replacement treatments [57]. Different neural cell subtypes such as cortical neurons, dopamine(DA)ergic, inhibitory gamma-aminobutyric-acid (GABA)ergic, and motor neurons can be generated from patient-derived iPSCs [99]. The iPSCs have also provided opportunities for understanding or even potentially reversing the disease pathology especially in neurodegenerative diseases [141–143]. Despite the known potentials of patient-derived iPSCs for understanding molecular targets and subsequently develop the hopes for treatment and drug discovery, there are some remaining challenges. Cell identity problems, safety, and purity issues along with long-term risks are some of these issues [17]. Hereupon, mesenchymal stem cells (MSCs) as multipotent cells (harvested from various tissues, i.e., umbilical cord blood, bone marrow, and adipose tissue) are multipotent progenitors which can be used for cell therapy of different neurological disorders (N [53, 88]. MSCs have some great features that make them proper for treating neurological diseases including their migration to the malignant sites which have beneficial effects in brain tumor. They also provide immunosuppressive properties with useful effects on inflammation-related neurological disorders. MSCs can also restore impaired neural tissue in neural injury causes of neurological disorders (N [88]. Thus, they have shown an ability to modulate immune responses. Promoting angiogenesis and restoring BBB integrity can be mentioned as other benefits of their application [71]. Transplantation of human MSCs has also shown neuroprotection effects and better neurological function after irradiation in mice [129]. But, safety challenges should be eliminated. Also, efficacy and mode of action of MSCs should be more widely found in clinical trials to achieve more reliable results [71]. Neural stem cells (NSCs) also have multipotential ability to grow indefinitely especially to provide three major cell types of CNS including neurons, astrocytes, and oligodendrocytes [135]. In neural injuries, transplanted NSCs can differentiate into neurons/glia and modulate motor dysfunction following by injury [111]. It has been also found that NSCs can act as an ideal candidate in the field of gene transfer therapy in neurological disorders [62]. Self-renewal capacity, proper histocompatibility with low immunogenicity, and the multi-directional potential of differentiation are features of them. It has been also found that exogenous NSCs in combination or overexpressing

with brain-derived neurotrophic-factor (BDNF), vascular endothelial growth-factor (VEGF), and nerve growth-factor (NGF) may lead to better results. NSCs can either supplement necrotic nerve cells or participate in repair mechanisms [152]. Contrary to ESCs and iPSCs, the probable tumorigenic effect of NSCs has not been found yet. However, their abnormal proliferation following in vivo transplantation may cause tumors. Producing stem cells in a large-scale, potential allogeneic rejection, survival efficiency of cell transplantation, challenges in administrating routes, and targeting issues are other remain challenges of NSC application [24, 152].

### Neurological Disorders Benefit from Stem Cell Therapy

The effects of stem cell-based therapies in the treatment of many neurological disorders such as Parkinson's disease, Huntington's disease, stroke, traumatic brain injury [63], multiple sclerosis (MS), multiple system atrophy, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, spinal cord injury, brain tumor, lysosomal storage diseases [92], epilepsy [89], and ataxia [141–143] have been supported. Herein, the use of stem cell therapy in some of them especially those that have been introduced as possible neurological complications of COVID-19 [137] is reviewed:

*Parkinson's disease:* Neurodegeneration of DA neurons — of substantia nigra pars compacta — (with unknown cause mostly) and the accumulations of eosinophilic inclusions are the main pathological characteristics of Parkinson's disease [131]. ESCs, iPSCs, NSCs, and MSCs can be mentioned as the most likely sources for stem cell therapy in Parkinson's disease. Stem cell biotechnologies regarding NSC and MSCs grafts have effects on the treatment management in direct and indirect repair pathways. Inducing endogenous neurogenesis, DA release, and DA neuron differentiation, as well as neural circuit integration and striatum reinnervation, are some of their effects on the direct repair pathways. Indirect repair pathways encompass expressing neurotrophic factors including cerebral dopamine neurotrophic factor (CDNF), NGF, BDNF, and glial-derived neurotrophic factor (GDNF), in addition to the facilitating DA neuronal maintenance and differentiation [34].

*Huntington's disease:* Huntington's disease is a neurodegenerative disorder, with autosomal dominant inheritance caused by an unstable expansion of CAG repeats within a huntingtin protein [18, 138]. Extensive loss in neurons of cerebral cortex and striatum can be another pathological feature of the disease. In this regard, successful use of stem cell-based medicine for the treatment of Huntington's disease has been reported. It has been

found that among different sources of stem cells used for neurological disorders, NSCs were preferably used in experimental studies for Huntington's disease due to their clear capacity for becoming neurons or glial cells after transplantation and inducing functional recovery. Lost neuron populations may be replaced according to the intrastriatal transplantation of GABAergic neurons leading to the restored functionality of the damaged circuits [61].

*Alzheimer's disease:* Extracellular amyloid-beta peptide leading to the amyloid plaque formation and neuronal loss can be mentioned as the most important characteristics of Alzheimer's disease [59, 72]. Stem cell therapy for Alzheimer's disease can promote regeneration of neurons and repair injured neurons. It can also lead to enhanced synaptogenesis in addition to the effects on higher amyloid-beta degradation [139]. MSCs and NSCs are the most commonly sources of stem cells used for transplantation. MSCs have been shown to have the advantages of promoting anti-inflammatory responses, angiogenic effects, and ease of isolation, whereas better neurogenesis and neuroprotective influences are mentioned about NSC advantages [117].

*Brain ischemic stroke:* According to the irreversible loss of neurons and neural tissue damage during brain ischemic stroke, stem cell therapy seems to be a hopeful treatment strategy [152]. ESCs, iPSCs, NSCs, and MSCs have been used in different animal studies of stroke treatment. In this regard, stem cell therapy has shown beneficial therapeutic effects for stroke according to its ability for cell replacement and neuroprotection. Angiogenesis, endogenous neurogenesis, and their capacity to attenuate inflammatory and immune responses are other mentioned benefits of stem cell therapy in this field. Many animal studies have been shown repaired neuronal function after transplantation [48]. Moreover, exosomes derived from NSC have been stated to have beneficial effects in the field of stem cell-based medicine that can overcome many challenges of this field [152]. As an example, some clinical trials in the field of brain stroke with the aim of utilizing stem cells are concluded in Table 1.

*Epilepsy:* Epileptogenic changes and hippocampal degeneration following epilepsy have shown promising changes (including improved cognitive dysfunction and ameliorated seizure) due to the stem cell therapy approaches [42, 43]. Repairing neural network by replacement of impaired neurons and promoting the survival of them are some benefits that can be mentioned for stem cell therapy in epilepsy [128]. ESCs, MSCs, and human iPSCs are the mentioned sources for this cell therapy [42, 43]. Moreover, NSCs and neural progenitors (NPs) have shown promising results regarding the great capacity of self-renewal and their ability for integrating into brain



**Table 1** Some stem cell-based clinical trials for stroke (<https://clinicaltrials.gov/>)

Study title	Condition	Intervention/treatment	Phase	Identifier number
<i>Autologous Bone Marrow Stem Cells in Middle Cerebral Artery Acute Stroke Treatment</i>	<i>Stroke, acute infarction, middle cerebral artery</i>	<i>Infusion on autologous CD34+ stem cells into middle cerebral artery</i>	<i>Phase 1 Phase 2</i>	<i>NCT00761982</i>
<i>Efficacy Study of CD34 Stem Cell in Chronic Stroke Patients</i>	<i>Stroke, middle cerebral artery infarction</i>	<i>Intercerebral implantation of autologous stem cells and convention therapy</i>	<i>Phase 2</i>	<i>NCT00950521</i>
<i>A Study of Allogeneic Mesenchymal Bone Marrow Cells in Subjects With Ischemic Stroke</i>	<i>Ischemic stroke</i>	<i>Allogeneic adult mesenchymal bone marrow stem cells</i>	<i>Phase 1 Phase 2</i>	<i>NCT01297413</i>
<i>Intraarterial Stem Cells in Subacute Ischemic Stroke</i>	<i>Ischemic stroke, middle cerebral artery infarction</i>	<i>Infusion of autologous bone marrow-derived mononuclear cells and standard care</i>	<i>Phase 1</i>	<i>NCT03080571</i>
<i>Cord Blood Infusion for Ischemic Stroke</i>	<i>Stroke</i>	<i>Allogeneic umbilical cord blood</i>	<i>Phase 1</i>	<i>NCT02397018</i>
<i>Clinical Trial Study About Human Adipose-Derived Stem Cells in the Stroke</i>	<i>Stroke</i>	<i>Adipose-derived stem cell injections</i>	<i>Phase 1</i>	<i>NCT02813512</i>
<i>A Clinical Study of iNSC Intervent Cerebral Hemorrhagic Stroke</i>	<i>Stroke, ischemic</i>	<i>Induction of neural stem cells</i>	<i>Early phase 1</i>	<i>NCT03725865</i>
<i>A Safety and Tolerability Study of Neural Stem Cells (NR1) in Subjects With Chronic Ischemic Subcortical Stroke (ISS)</i>	<i>Ischemic stroke</i>	<i>Neural stem cells</i>	<i>Phase 1, Phase 2</i>	<i>NCT04631406</i>

circuitry. It can cause hopeful results especially in some types of epilepsy associated with loss or malfunction of specific neurons of specific brain structures. Embryonic blastocyst, and adult and fetal brain in addition to the non-neural tissues can be mentioned as potential sources [112].

**Ataxia:** The cerebellar ataxias encompass different neurological disorders introduced by motor coordination loss as a cause of neuron degeneration in the brainstem, spinocerebellar tracts, and cerebellar cortex [64]. Although there are not a lot of researches worked on using stem cells for modeling and treatment of cerebellar ataxia, iPSC-based models are mentioned to be hopeful approaches to find out disease progression processes and also to develop early-intervention treatment strategies [141–143]. MSCs have also shown effective results in some mouse models of cerebellar ataxia by promoting synaptic connection, inducing neuronal growth, and reducing apoptosis as the results of secreting innate factors [90].

### Stem Cell-Based Biotechnology: a Promising Approach for COVID-19-Associated Neurological Disorders

As it was mentioned, COVID-19 may be associated with neurological complications. SARS-CoV-2 infection may be followed by probable impairment of the neuraxis, virtually

in any part of it. Herein, direct invasion, triggered metabolic abnormalities, and autoimmune responses to the viral infection may result in neurological diseases [19]. Increased risk of neurodegenerative diseases and dementia as well as other mentioned neurological complications related to CNS (such as headache, dizziness, impaired consciousness, acute cerebrovascular disease, and epilepsy) and PNS (such as hyposmia/anosmia, hypogeusia/ageusia, and GBS) can be stated as these neurological complications [93, 94, 137]. Human neurological disorders whether neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease or other types like brain stroke are associated with neuron and glial cell loss of CNS. In this regard, stem cell-based biotechnologies have been noticed as interesting approaches for the treatment of these disorders in different ways of generating neurons and glial cells, attenuating some abnormalities in animal models of neurological disorders, and even in clinical level on patients. They can do their functions through cell replacement, their trophic actions, and by modifying inflammatory [83]. Utilizing an effective therapeutic approach requires a sufficient understanding of different aspects of the neurological disorders regarding their pathophysiology which was mentioned before. The functional features of stem cell strategies and their various influences regarding their different types should be also known. According to the histological and functional data obtained from animal studies, the most appropriate stem cell type and strategy can be designed [149]. More than 200 clinical studies have

been conducted that mainly focus on using stem cells for the treatment of MS, stroke, and spinal cord injuries as neurological disorders [10, 11]. Human ESCs and human iPSCs as pluripotent stem cells can be used in the field of neurodegenerative disorders. Although ESCs contain optimal cell sources for cell-replacement treatments, eliminating any danger of contamination and solving existing ethical issues are remaining challenges [75, 83]. The iPSCs can be used as neurodegenerative disease models and for autologous transplantation which does not need immuno-suppressive therapies and does not bring ethical challenges (because of their sources of somatic cells). The iPSCs with similar characteristics to ESCs (including morphology, differentiation potential, and gene expression profile) have also the same and even more challenges than ESCs including significant reprogramming variability and the higher risks of tumor formation [76, 83]. Human MSCs, as multipotent stem cells, have both paracrine and autocrine functions in impaired tissues and can modulate inflammation. Relatively easy expansion with no ethical issues and their migration ability to the brain damaged areas are other features of them [78, 79]. Human hematopoietic stem cells (HSCs) are other types of multipotent stem cells that have benefits in promoting neo-vascularization and in hemostasis maintenance with no ethical concerns. But, consistency of number and cells' potency in addition to the needing for "ex vivo" expansion of cells are some possible challenges [83, 132]. NSCs, neural crest stem cells (NCSCs), human dental pulp stem cells (DPSCs), human epidermal neural crest stem cells (EPI-NCSCs), and olfactory ensheathing glia are other multipotent stem cells which have the neurogenic potential [73]. The safety profile of NSCs seems to be good but it is largely unknown. Their application can be associated with minor ethical concerns according to the sources of them [51]. The direct production of induced neural stem cells (iNSCs) from the conversion of mouse somatic cells can be also provided opportunities for disease modeling and therapeutic options (in the field of neurological disorders) with more therapeutic applicability [77]. Despite the considerable developments of stem cell-based biotechnologies in the treatment of neurological disorders, there are still some challenges and questions should be answered including the ideal source for cellular grafts; because there are different sources that neurons can be harvested from including NSCs, ESC, umbilical cord blood hematopoietic stem cells, bone marrow MSCs, and iPSC. Safety issues according to the risks of tumorigenicity should be also solved. It has been also found that ESCs or NSC-derived cell types may be associated with other neuronal or glial cells leading to the unwanted interactions among transplanted cells or with host neurons [63]. Taken together, stem cell-based approaches have provided hopeful strategies for the treatment of various disorders especially those that do not have definite effective therapeutic approaches.

Stroke, amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease as some of the neurological involvements are some of these mentioned disorders that may benefit from stem cell-related strategies [78, 79]. Also, as it was mentioned earlier, neurological events can be mentioned as important COVID-19 complications [60]. Indeed, COVID-19 infection can be associated with multiple neurological manifestations, although the causative link or true incidence has not been established yet. The characteristics of immunoactive treatments and other therapeutic approaches have been explained so far. But, novel therapeutic strategies are still required [49]. In this regard, stem cell-based approaches could be defined as hopeful therapeutic approaches for the treatment of these COVID-19 neurological complications according to their previous successful applying in similar neurological disorders.

## Conclusion and Future Perspectives

Due to the destructive effects of CNS and PNS involvement following COVID-19, health planners need to be conscious of the rising burdens. Accordingly, this is considered the important focus of most modern news. Herein, accretive clinical, symptomatic, and epidemiological examinations via collaboration of clinicians and scientists are expected to help characterize the neurological manifestations and complications [56, 93, 94]. On the other hand, the importance of studying to find the best and most modern treatment methods is also undeniable. Today's cell-based therapeutics are considered a revolutionary approach in treatment. New research in this area is based on the launch of smart cell therapy. Accordingly, the future smart cell treatments should be advantageously adjustable, have characteristic harmfulness decreasing the executives' frameworks, and have the option to settle quickly changing disease resolution prevention mechanisms.

**Author Contribution** All the authors contributed to the study conception and design. Peyvand Parhizkar Roudsari and Sepideh Alavi-Moghadam wrote the first draft. Mostafa Rezaei-Tavirani and Akram Tayanloo-Beik helped to study and gather information. Neda Mehrdad and Hossein Adibi extensively edited the manuscript. Bagher Larjani participated in a critical review. Babak Arjmand helped supervise the project and gave final approval of the version to be published.

**Data Availability** Not applicable.

**Code Availability** Not applicable.

## Declarations

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Conflict of Interest** The authors declare no competing interests.

## References

- Abdel-Hamid H, Oddis CV, Lacomis D. Severe hydroxychloroquine myopathy. *Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine*. 2008;38(3):1206–10.
- Abdin SM, Elgendy SM, Alyammahi SK, Alhamad DW, Omar HA. Tackling the cytokine storm in COVID-19, challenges and hopes. *Life Sciences*. 2020;257:118054.
- Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. *J Neurol* 2020:1–38.
- Achar A, Ghosh C. COVID-19-associated neurological disorders: the potential route of CNS invasion and blood-brain relevance. *Cells*. 2020 9(11).
- Afshar L, Aghayan HR, Sadighi J, Arjmand B, Hashemi SM, Basiri M, Samani RO, Ashtiani MK, Azin SA, Hajizadeh-Saffar E, Gooshki ES, Hamidieh AA, Rezaia Moallem MR, Azin SM, Shariatinasab S, Soleymani-Goloujeh M, Baharvand H. Ethics of research on stem cells and regenerative medicine: ethical guidelines in the Islamic Republic of Iran. *Stem Cell Res Ther*. 2020;11(1):396.
- Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: a review. *Neurocritical Care* 2020.
- Aghayan HR, Soleimani M, Goodarzi P, Norouzi-Javidan A, Emami-Razavi SH, Larijani B, Arjmand B. Magnetic resonance imaging of transplanted stem cell fate in stroke. *J Res Med Sci*. 2014;19(5):465.
- Ahmed MU, Hanif M, Ali MJ, Haider MA, Kherani D, Memon GM, Karim AH, Sattar A. Neurological manifestations of COVID-19 (SARS-CoV-2): a review. *Front Neurol*. 2020;11:518.
- Ai L, Jiang L, Xu Z, Yan H, Luo P, He Q. COVID-19 epidemic: a special focus on diagnosis, complications, and management. *Expert Rev Clin Pharmacol*. 2020;13(10):1085–93.
- Alessandrini M, Preynat-Seauve O, Bruin KD, Pepper MS. Stem cell therapy for neurological disorders. *South African Medical Journal*. 2019;109(8 Supplement 1):S71–8.
- Alessandrini M, Preynat-Seauve O, De Bruin K, Pepper MS. Stem cell therapy for neurological disorders. *S Afr Med J*. 2019;109(8b):70–7.
- Antonelli A, Elia G, Ferrari SM, Foddis R, De Marco S, Cristaudo A, Fallahi P. The COVID-19, epidemiology, clinic and prevention. *Curr Genomics*. 2020;21(3):157–157.
- Arjmand B, Ghorbani F, Koushki M, Rezaei-Tavirani M. Gastrointestinal symptoms in patients with mild and severe COVID-19: a scoping review and meta-analysis. *Gastroenterology and hepatology from bed to bench*. 2020;13(4):321.
- Arjmand B, Goodarzi P, Aghayan H, Payab M, Rahim F, Alavi-Moghadam S, Mohamadi-Jahani F, Larijani B. Co-transplantation of human fetal mesenchymal and hematopoietic stem cells in type 1 diabetic mice model. *Front Endocrinol*. 2019;10:761.
- Arjmand B, Sarvari M, Alavi-Moghadam S, Payab M, Goodarzi P, Gilany K, Mehrdad N, Larijani B. Prospect of stem cell therapy and regenerative medicine in osteoporosis. *Front Endocrinol* 2020;11.
- Azodi MZ, Arjmand B, Zali A, Razzaghi M. Introducing APOA1 as a key protein in COVID-19 infection: a bioinformatics approach. *Gastroenterology and hepatology from bed to bench*. 2020;13(4):367.
- Barral S, Kurian MA. Utility of induced pluripotent stem cells for the study and treatment of genetic diseases: focus on childhood neurological disorders. *Front Mol Neurosci*. 2016;9:78.
- Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, Nance M, Ross CA, Scahill RI, Wetzel R, Wild EJ, Tabrizi SJ. Huntington disease *Nature. Reviews Disease Primers*. 2015;1(1):15005.
- Berger JR. COVID-19 and the nervous system. *J Neurovirol*. 2020;26(2):143–8.
- Blum B, Benvenisty N. The tumorigenicity of human embryonic stem cells. *Advances in Cancer Research*, Academic Press. 2008;100:133–58.
- Bobker SM, Robbins MS. COVID-19 and headache: a primer for trainees. *Headache*. 2020;60(8):1806–11.
- Bodro M, Compta Y, Sánchez-Valle R. Presentations and mechanisms of CNS disorders related to COVID-19. *Neurol Neuroimmunol Neuroinflamm* 2021;8(1).
- Bozdağ SC, Yüksel MK, Demirer T. Adult stem cells and medicine. *Adv Exp Med Biol*. 2018;1079:17–36.
- Broughton BR, Lim R, Arumugam TV, Drummond GR, Wallace EM, Sobey CG. Post-stroke inflammation and the potential efficacy of novel stem cell therapies: focus on amnion epithelial cells. *Front Cell Neurosci*. 2012;6:66.
- Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. *Rev Neurol*. 2020;70(9):311–22.
- Carrillo-Larco RM, Altez-Fernandez C. Anosmia and dysgeusia in COVID-19: a systematic review. *Wellcome Open Res*. 2020;5:94.
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, J. a. Xia, T. Yu, X. Zhang and L. Zhang,. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)*. 2020;395(10223):507–13.
- Choudhery MS, Harris DT. Stem cell therapy for COVID-19: possibilities and challenges. *Cell Biol Int*. 2020;44(11):2182–91.
- Davis GF. Adverse effects of corticosteroids: II Systemic. *Clinics in dermatology*. 1986;4(1):161–9.
- de Lucena TMC, da Silva Santos AF, de Lima BR, de Albuquerque Borborema ME, de Azevedo Silva J. Mechanism of inflammatory response in associated comorbidities in COVID-19. *Diabetes Metab Syndr*. 2020;14(4):597–600.
- de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*. 2016;14(8):523–34.
- Derakhshanrad N, Saberi H, Meybodi KT, Taghvaei M, Arjmand B, Aghayan HR, Kohan AH, Haghpanahi M, Rahmani S. Case report: combination therapy with mesenchymal stem cells and granulocyte-colony stimulating factor in a case of spinal cord injury. *Basic and clinical neuroscience*. 2015;6(4):299.
- Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfecting with 2019 novel coronavirus and influenza virus in Wuhan China. *Journal of medical virology*. 2020;92(9):1549–55.
- Fu M-H, Li C-L, Lin H-L, Chen P-C, Calkins MJ, Chang Y-F, Cheng P-H, Yang S-H. Stem cell transplantation therapy in Parkinson's disease. *Springerplus*. 2015;4:597–597.
- Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology*. 2020;58(3):299–301.
- Gevers S, Kwa M, Wijnans E, Van Nieuwkoop C. Safety considerations for chloroquine and hydroxychloroquine in the treatment of COVID-19. *Clin Microbiol Infect*. 2020;26(9):1276–7.
- Ghasemiyeh P, Borhani-Haghighi A, Karimzadeh I, Mohammedi-Samani S, Vazin A, Safari A, Qureshi AI. Major neurologic adverse drug reactions, potential drug-drug interactions and pharmacokinetic aspects of drugs used in COVID-19

- patients with stroke: a narrative review. *Ther Clin Risk Manag.* 2020;16:595–605.
38. Ghodsi M, Heshmat R, Amoli M, Keshtkar AA, Arjmand B, Aghayan H, Hosseini P, Sharifi AM, Larijani B. The effect of fetal liver-derived cell suspension allotransplantation on patients with diabetes: first year of follow-up. *Acta Med Iran.* 2012;50(8):541–6.
  39. Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *Med J Aust.* 2020;213(2):54–6.
  40. Goodarzi P, Aghayan HR, Larijani B, Soleimani M, Dehpour A-R, Sahebjam M, Ghaderi F, Arjmand B. Stem cell-based approach for the treatment of Parkinson's disease. *Med J Islam Repub Iran.* 2015;29:168.
  41. Goodarzi P, Aghayan HR, Payab M, Larijani B, Alavi-Moghadam S, Sarvari M, Adibi H, Khatami F, Heravani NF, Hada-vandkhani M, Arjmand B. Human fetal skin fibroblast isolation and expansion for clinical application. *Methods Mol Biol.* 2020;2109:261–73.
  42. Goodarzi P, Aghayan HR, Soleimani M, Norouzi-Javidan A, Mohamadi-Jahani F, Jahangiri S, Emami-Razavi SH, Larijani B, Arjmand B. Stem cell therapy for treatment of epilepsy. *Acta Medica Iranica* 2014;651–655.
  43. Goodarzi P, Aghayan HR, Soleimani M, Norouzi-Javidan A, Mohamadi-Jahani F, Jahangiri S, Emami-Razavi SH, Larijani B, Arjmand B. Stem cell therapy for treatment of epilepsy. *Acta Med Iran.* 2014;52(9):651–5.
  44. Goodarzi P, Alavi-Moghadam S, Sarvari M, Beik AT, Falahzadeh K, Aghayan H, Payab M, Larijani B, Gilany K, Rahim F. Adipose tissue-derived stromal cells for wound healing. *Cell Biology and Translational Medicine, Volume 4, Springer; 2018.* pp133–149.
  45. Goodarzi P, Falahzadeh K, Aghayan H, Payab M, Larijani B, Alavi-Moghadam S, Tayanloo-Beik A, Adibi H, Gilany K, Arjmand B. Therapeutic abortion and ectopic pregnancy: alternative sources for fetal stem cell research and therapy in Iran as an Islamic country. *Cell Tissue Banking.* 2019;20(1):11–24.
  46. Goodarzi P, Larijani B, Alavi-Moghadam S, Tayanloo-Beik A, Mohamadi-Jahani F, Ranjbaran N, Payab M, Falahzadeh K, Mousavi M, Arjmand B. Mesenchymal stem cells-derived exosomes for wound regeneration. *Cell Biology and Translational Medicine, Volume 4, Springer; 2018.* p. 119–131.
  47. Goodarzi P, Payab M, Alavi-Moghadam S, Larijani B, Rahim F, Bana N, Sarvari M, Adibi H, Heravani NF, Hadavandkhani M. Development and validation of Alzheimer's disease animal model for the purpose of regenerative medicine. *Cell Tissue Banking.* 2019;20(2):141–51.
  48. Hao L, Zou Z, Tian H, Zhang Y, Zhou H, Liu L. Stem cell-based therapies for ischemic stroke. *Biomed Res Int.* 2014;2014:468748.
  49. Hartung H-P, Aktas O. COVID-19 and management of neuroimmunological disorders. *Nat Rev Neurol.* 2020;16(7):347–8.
  50. Helms J, Kremer S, Merdji H, Schenck M, Severac F, Clere-Jehl R, Studer A, Radosavljevic M, Kummerlen C, Monnier A. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care.* 2020;24(1):1–11.
  51. Hess DC, Borlongan CV. Stem cells and neurological diseases. *Cell Prolif.* 2008;41(s1):94–114.
  52. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. *Transl Stroke Res.* 2020;11(3):322–5.
  53. Hima Bindu A, Srilatha B. Potency of various types of stem cells and their transplantation. *J Stem Cell Res Ther.* 2011;1:115.
  54. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. *Lancet.* 2020;395(10223):497–506.
  55. Hughes JT, Esiri M, Oxbury J, Whitty C. Chloroquine myopathy. *QJM: An International Journal of Medicine* 1971;40(1):85–93.
  56. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. *Cell.* 2020
  57. Ito D, Okano H, Suzuki N. Accelerating progress in induced pluripotent stem cell research for neurological diseases. *Ann Neurol.* 2012;72(2):167–74.
  58. Joannides A, Chandran S. Human embryonic stem cells: an experimental and therapeutic resource for neurological disease. *J Neurol Sci.* 2008;265(1–2):84–8.
  59. Kang JM, Yeon BK, Cho S-J, Suh Y-H. Stem cell therapy for Alzheimer's disease: a review of recent clinical trials. *Journal of Alzheimer's Disease.* 2016;54(3):879–89.
  60. Kanwar D, Baig AM, Wasay M. Neurological manifestations of COVID-19. *J Pak Med Assoc.* 2020;70(Suppl 3 5):S101-s103.
  61. Kim M, Lee S-T, Chu K, Kim SU. Stem cell-based cell therapy for Huntington disease: a review. *Neuropathology.* 2008;28(1):1–9.
  62. Kim SU. Human neural stem cells genetically modified for brain repair in neurological disorders. *Neuropathology.* 2004;24(3):159–71.
  63. Kim SU, de Vellis J. Stem cell-based cell therapy in neurological diseases: a review. *J Neurosci Res.* 2009;87(10):2183–200.
  64. Klockgether T. Update on degenerative ataxias. *Curr Opin Neurol.* 2011;24(4):339–45.
  65. Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer PY, Lepiller Q, Gendrin V, Zayet S. Features of anosmia in COVID-19. *Medicine et maladies infectieuses.* 2020;50(5):436–9.
  66. Kow CS, Aldeyab M, Hasan SS. Quality of adverse event reporting in clinical trials of remdesivir in patients with COVID-19. *Eur J Clin Pharmacol.* 2020.
  67. Lao WP, Imam SA, Nguyen SA. Anosmia, hyposmia, and dysgeusia as indicators for positive SARS-CoV-2 infection. *World journal of otorhinolaryngology - head and neck surgery.* 2020. <https://doi.org/10.1016/j.wjorl.2020.1004.1001>.
  68. Larijani B, Goodarzi P, Payab M, Tayanloo-Beik A, Sarvari M, Gholami M, Gilany K, Nasli-Esfahani E, Yarahmadi M, Ghaderi F. The design and application of an appropriate Parkinson's disease animal model in regenerative medicine. 2019
  69. Larijani B, Heravani NF, Alavi-Moghadam S, Goodarzi P, Rezaei-Tavirani M, Payab M, Gholami M, Razi F, Arjmand B. Cell therapy targets for autism spectrum disorders: hopes, challenges and future directions. 2020
  70. Larijani B, Roudsari PP, Hadavandkhani M, Alavi-Moghadam S, Rezaei-Tavirani M, Goodarzi P, Sayahpour FA, Mohamadi-Jahani F, Arjmand B. Stem cell-based models and therapies: a key approach into schizophrenia treatment. *Cell Tissue Banking.* 2021;22:1–17.
  71. Laroni A, de Rosbo NK, Uccelli A. Mesenchymal stem cells for the treatment of neurological diseases: immunoregulation beyond neuroprotection. *Immunol Lett.* 2015;168(2):183–90.
  72. Lee HJ, Lee JK, Lee H, Shin JW, Carter JE, Sakamoto T, Jin HK, Bae JS. The therapeutic potential of human umbilical cord blood-derived mesenchymal stem cells in Alzheimer's disease. *Neurosci Lett.* 2010;481(1):30–5.
  73. Leong WK, Henshall TL, Arthur A, Kremer KL, Lewis MD, Helps SC, Field J, Hamilton-Bruce MA, Warming S, Manavis J. Human adult dental pulp stem cells enhance poststroke functional recovery through non-neural replacement mechanisms. *Stem Cells Transl Med.* 2012;1(3):177–87.
  74. Li Z, Niu S, Guo B, Gao T, Wang L, Wang Y, Wang L, Tan Y, Wu J, Hao J. Stem cell therapy for COVID-19, ARDS and pulmonary fibrosis. *Cell Prolif.* 2020;53(12):e12939.
  75. Liras A. Future research and therapeutic applications of human stem cells: general, regulatory, and bioethical aspects. *J Transl Med.* 2010;8(1):131.
  76. Lister R, Pelizzola M, Kida YS, Hawkins RD, Nery JR, Hon G, Antosiewicz-Bourget J, O'Malley R, Castanon R, Klugman

- S. Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells. *Nature*. 2011;471(7336):68–73.
77. Liu G-H, Yi F, Suzuki K, Qu J, Belmonte JCI. Induced neural stem cells: a new tool for studying neural development and neurological disorders. *Cell Res*. 2012;22(7):1087–91.
  78. Liu R, Zhang Z, Lu Z, Borlongan C, Pan J, Chen J, Qian L, Liu Z, Zhu L, Zhang J. Human umbilical cord stem cells ameliorate experimental autoimmune encephalomyelitis by regulating immunoinflammation and remyelination. *Stem cells and development*. 2013;22(7):1053–62.
  79. Liu S-P, Fu R-H, Huang S-J, Huang Y-C, Chen S-Y, Chang C-H, Liu C-H, Tsai C-H, Shyu W-C, Lin S-Z. Stem cell applications in regenerative medicine for neurological disorders. *Cell Transplant*. 2013;22(4):631–7.
  80. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, Mu J, Guo J, Li W, Wang G, Gao H, Zhang Y, Lin M, Chen L, Shen S, Zhang H, Sander JW, Luo J, Chen S, Zhou D. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. *Epilepsia*. 2020;61(6):e49–53.
  81. Magdy R, Hussein M, Ragaie C, Abdel-Hamid HM, Khallaf A, Rizk HI, Dahshan A. Characteristics of headache attributed to COVID-19 infection and predictors of its frequency and intensity: a cross sectional study. *Cephalalgia: an international journal of headache*. 2020;40(13):1422–31.
  82. Mahalaxmi I, Kaavya J, Mohana Devi S, Balachandar V. COVID-19 and olfactory dysfunction: a possible associative approach towards neurodegenerative diseases. *J Cell Physiol*. 2021;236(2):763–70.
  83. Martínez-Morales PL, Revilla A, Ocaña I, González C, Sainz P, McGuire D, Liste I. Progress in stem cell therapy for major human neurological disorders. *Stem Cell Reviews and Reports*. 2013;9(5):685–99.
  84. Mimeault M, Hauke R, Batra SK. Stem cells: a revolution in therapeutics—recent advances in stem cell biology and their therapeutic applications in regenerative medicine and cancer therapies. *Clin Pharmacol Ther*. 2007;82(3):252–64.
  85. Moghaddam SA, Yousefi B, Sanooghi D, Faghihi F, Roodbari NH, Bana N, Joghataei MT, Pooyan P, Arjmand B. Differentiation potential of human CD133 positive hematopoietic stem cells into motor neuron-like cells, in vitro. *J Chem Neuroanat*. 2017;86:35–40.
  86. Morawska L, Tang JW, Bahnfleth W, Bluyssen PM, Boerstra A, Buonanno G, Cao J, Dancer S, Floto A, Franchimon F, Haworth C, Hogeling J, Isaxon C, Jimenez JL, Kurnitski J, Li Y, Loomans M, Marks G, Marr LC, Mazzarella L, Melikov AK, Miller S, Milton DK, Nazaroff W, Nielsen PV, Noakes C, Peccia J, Querol X, Sekhar C, Seppänen O, Tanabe S-I, Tellier R, Tham KW, Wargoock P, Wierzbicka A, Yao M. How can airborne transmission of COVID-19 indoors be minimised? *Environment International*. 2020;142:105832.
  87. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *American Journal of Physiology-Endocrinology and Metabolism*. 2020;318(5):E736–41.
  88. Momin N, E., A. Mohyeldin, H. A Zaidi, G. Vela and A. Quiñones-Hinojosa. Mesenchymal stem cells: new approaches for the treatment of neurological diseases. *Curr Stem Cell Res Ther*. 2010;5(4):326–44.
  89. Naegele JR, Vemuri MC, Studer L. Embryonic stem cell therapy for intractable epilepsy. Jasper's basic mechanisms of the epilepsies. J. L. Noebels, M. Avoli, M. A. Rogawski, R. W. Olsen and A. V. Delgado-Escueta. Bethesda (MD), National Center for Biotechnology Information (US) Copyright © 2012, Michael A Rogawski, Antonio V Delgado-Escueta, Jeffrey L Noebels, Massimo Avoli and Richard W Olsen. 2012
  90. Nakamura K, Mieda T, Suto N, Matsuura S, Hirai H. Mesenchymal stem cells as a potential therapeutic tool for spinocerebellar ataxia. *The Cerebellum*. 2015;14(2):165–70.
  91. Naserghandi A, Allameh SF, Saffarpour R. All about COVID-19 in brief. *New Microbes New Infect*. 2020;35:100678.
  92. Nguyen H, Zariello S, Coats A, Nelson C, Kingsbury C, Gorsky A, Rajani M, Neal EG, Borlongan CV. Stem cell therapy for neurological disorders: a focus on aging. *Neurobiol Dis*. 2019;126:85–104.
  93. Niazkar HR, Zibae B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. *Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2020;41(7):1667–71.
  94. Niazkar HR, Zibae B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. *Neurol Sci* 2020;1
  95. Nikbakht F, Mohammadkhanizadeh A, Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. *Multiple sclerosis and related disorders*. 2020;46:102535–102535.
  96. O'Shaughnessy TJ, Zim B, Ma W, Shaffer KM, Stenger DA, Zamani K, Gross GW, Pancrazio JJ. Acute neuropharmacologic action of chloroquine on cortical neurons in vitro. *Brain Res*. 2003;959(2):280–6.
  97. Organization WH. Health system efficiency: how to make measurement matter for policy and management. Regional Office for Europe: World Health Organization; 2016.
  98. Orrù G, Conversano C, Malloggi E, Francesconi F, Ciacchini R, Gemignani A. Neurological complications of COVID-19 and possible neuroinvasion pathways: a systematic review. *Int J Environ Res Public Health*. 2020;17(18):6688.
  99. Pamies D, Barreras P, Block K, Makri G, Kumar A, Wiersma D, Smirnova L, Zang C, Bressler J, Christian KM, Harris G, Ming G-L, Berlinicke CJ, Kyro K, Song H, Pardo CA, Hartung T, Högberg HT. A human brain microphysiological system derived from induced pluripotent stem cells to study neurological diseases and toxicity. *Altex*. 2017;34(3):362–76.
  100. Parhizkar Roudsari P, Alavi-Moghadam S, Payab M, Sayahpour FA, Aghayan HR, Goodarzi P, Mohamadi-Jahani F, Larjani B, Arjmand B. Auxiliary role of mesenchymal stem cells as regenerative medicine soldiers to attenuate inflammatory processes of severe acute respiratory infections caused by COVID-19. *Cell Tissue Banking*. 2020;21(3):405–25.
  101. Pascarella G, Strumia A, Piliogo C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE. COVID-19 diagnosis and management: a comprehensive review. *J Intern Med*. 2020;288(2):192–206.
  102. Payab M, Goodarzi P, Heravani NF, Hadavandkhani M, Zarei Z, Falahzadeh K, Larjani B, Rahim F, Arjmand B. Stem cell and obesity: current state and future perspective. *Cell Biology and Translational Medicine*, Volume 2, 2018. Springer: 1–22.
  103. Paybast S, Emami A, Koosha M, Baghalha F. Novel coronavirus disease (COVID-19) and central nervous system complications: what neurologist need to know. *Acta Neurol Taiwan*. 2020;29(1):24–31.
  104. Ragab D, Salah Eldin H, Taeimah M, Khattab R Salem R. The COVID-19 cytokine storm; what we know so far. *Front Immunol* 2020;11(1446).
  105. Rahim F, Arjmand B. Stem cell clinical trials for multiple sclerosis: the past, present and future. *Neurological Regeneration*: Springer; 2017. p. 159–72.
  106. Rahim F, Arjmand B, Shirbandi K, Payab M, Larjani B. Stem cell therapy for patients with diabetes: a systematic review and meta-analysis of metabolomics-based risks and benefits. *Stem cell investigation*. 2018;5:40–40.
  107. Rahim, F., B. Arjmand, K. Shirbandi, M. Payab and B. Larjani. Stem cell therapy for patients with diabetes: a systematic review

- and meta-analysis of metabolomics-based risks and benefits. *Stem Cell Investig* 2018;5.
108. Rahim F, Arjmand B, Tirdad R, Malehi AS. Stem cell therapy for multiple sclerosis. *The Cochrane Database of Systematic Reviews* 2018;2018(6).
  109. Rahimi K. Guillain-Barre syndrome during COVID-19 pandemic: an overview of the reports. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2020;41(11):3149–56.
  110. Reinhard A, Ikonomidis C, Broome M, Gorostidi F. [Anosmia and COVID-19]. *Rev Med Suisse* 2020; 16(N° 691–2): 849–851.
  111. Riess P, Zhang C, Saatman KE, Laurer HL, Longhi LG, Raghupathi R, Lenzlinger PM, Lifshitz J, Boockvar J, Neugebauer E, Snyder EY, McIntosh TK. Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury. *Neurosurgery*. 2002;51(4):1043–54.
  112. Roper SN, Steindler DA. Stem cells as a potential therapy for epilepsy. *Exp Neurol*. 2013;244:59–66.
  113. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Coronavirus disease (COVID-19)—statistics and research. *Our World in data*. 2020
  114. Roudsari PP, Alavi-Moghadam S, Payab M, Sayahpour FA, Aghayan HR, Goodarzi P, Mohamadi-Jahani F, Larijani B, Arjmand B. Auxiliary role of mesenchymal stem cells as regenerative medicine soldiers to attenuate inflammatory processes of severe acute respiratory infections caused by COVID-19. *Cell and tissue banking*: 2020;1–21.
  115. Saberi H, Moshayedi P, Aghayan H-R, Arjmand B, Hosseini S-K, Emami-Razavi S-H, Rahimi-Movaghar V, Raza M, Firouzi M. Treatment of chronic thoracic spinal cord injury patients with autologous Schwann cell transplantation: an interim report on safety considerations and possible outcomes. *Neurosci Lett*. 2008;443(1):46–50.
  116. Sadeghi S, Soudi S, Shafiee A, Hashemi SM. Mesenchymal stem cell therapies for COVID-19: current status and mechanism of action. *Life Sci*. 2020;262:118493.
  117. Salem H, Colpo GD, Teixeira AL. Stem cells in Alzheimer's disease: current standing and future challenges. *Adv Exp Med Biol*. 2018;1079:93–102.
  118. Sanberg PR, Eve DJ, Cruz LE, Borlongan CV. Neurological disorders and the potential role for stem cells as a therapy. *Br Med Bull*. 2012;101(1):163–81.
  119. Saniasiaya J, Kulasegarah J. Dizziness and COVID-19. *Ear Nose Throat J*. 2021;100(1):29–30.
  120. Sheikh Hosseini M, Parhizkar Roudsari P, Gilany K, Goodarzi P, Payab M, Tayanloo-Beik A, Larijani B, Arjmand B. Cellular dust as a novel hope for regenerative cancer medicine. *Adv Exp Med Biol*. 2020;1288:139–60.
  121. Sheraton M, Deo N, Kashyap R, Surani S. A review of neurological complications of COVID-19. *Cureus*. 2020;12(5):e8192–e8192.
  122. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res*. 2020;24:91–8.
  123. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piccentini M, Ippolito G, Melino G. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ*. 2020;27(5):1451–4.
  124. Singh AK, Bhushan B, Maurya A, Mishra G, Singh SK, Awasthi R. Novel coronavirus disease 2019 (COVID-19) and neurodegenerative disorders. *Dermatologic Therapy* 2020;e13591.
  125. Singhal T. A review of coronavirus disease-2019 (COVID-19). *Indian J Pediatr*. 2020;87(4):281–6.
  126. Soleimani M, Aghayan HR, Goodarzi P, Hagh MF, Lajimi AA, Saki N, Jahani FM, Javidan AN, Arjmand B. Stem cell therapy-approach for multiple sclerosis treatment. *Arch Neurosci*. 2016;3(1):e21564.
  127. Song CG, Zhang YZ, Wu HN, Cao XL, Guo CJ, Li YQ, Zheng MH, Han H. Stem cells: a promising candidate to treat neurological disorders. *Neural Regen Res*. 2018;13(7):1294–304.
  128. Sørensen AT, Kokaia M. Novel approaches to epilepsy treatment. *Epilepsia*. 2013;54(1):1–10.
  129. Soria B, Martín-Montalvo A, Aguilera Y, Mellado-Damas N, López-Beas J, Herrera-Herrera I, López E, Barcia JA, Alvarez-Dolado M, Hmadcha A, Capilla-González V. Human mesenchymal stem cells prevent neurological complications of radiotherapy. *Front Cell Neurosci* 2019;13(204).
  130. Steardo L, Steardo Jr L, Zorec R, Verkhatsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiologica* 2020;e13473.
  131. Stoddard-Bennett T, Reijo Pera R. Treatment of Parkinson's disease through personalized medicine and induced pluripotent stem cells. *Cells* 2019;8(1).
  132. Taguchi A, Soma T, Tanaka H, Kanda T, Nishimura H, Yoshikawa H, Tsukamoto Y, Iso H, Fujimori Y, Stern DM. Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model. *J Clin Investig*. 2004;114(3):330–8.
  133. Taherifard E, Taherifard E. Neurological complications of COVID-19: a systematic review. *Neurol Res*. 2020;42(11):905–12.
  134. Tancheva L, Petralia MC, Miteva S, Dragomanova S, Solak A, Kalfin R, Lazarova M, Yarkov D, Ciurleo R, Cavalli E. Emerging neurological and psychobiological aspects of COVID-19 infection. *Brain Sci*. 2020;10(11):852.
  135. Temple S. The development of neural stem cells. *Nature*. 2001;414(6859):112–7.
  136. Ticinesi A, Cerundolo N, Parise A, Nouvenne A, Prati B, Guerra A, Lauretani F, Maggio M, Meschi T. Delirium in COVID-19: epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. *Aging Clin Exp Res*. 2020;32(10):2159–66.
  137. Verkhatsky A, Li Q, Melino S, Melino G, Shi Y. Can COVID-19 pandemic boost the epidemic of neurodegenerative diseases? *Biol Direct*. 2020;15(1):28.
  138. Vonsattel JPG, DiFiglia M. Huntington disease. *J Neuropathol Exp Neurol*. 1998;57(5):369.
  139. Wang S-M, Lee C-U, Lim HK. Stem cell therapies for Alzheimer's disease: is it time? *Curr Opin Psychiatry*. 2019;32(2):105–16.
  140. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc*. 2006;81(10):1361–7.
  141. Watson LM, Wong MM, Becker EB. Induced pluripotent stem cell technology for modelling and therapy of cerebellar ataxia. *Open Biol*. 2015;5(7):150056.
  142. Watson LM, Wong MM, Becker EB. Induced pluripotent stem cell technology for modelling and therapy of cerebellar ataxia. *Open biology*. 2015;5(7):150056.
  143. Watson LM, Wong MM, Becker EBE. Induced pluripotent stem cell technology for modelling and therapy of cerebellar ataxia. *Open Biology*. 2015;5(7):150056.
  144. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. *Infection* 2020
  145. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, Liu C, Yang C. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, behavior, and immunity* 2020
  146. Yazdanpanah N, Saghadzadeh A, Rezaei N. Anosmia: a missing link in the neuroimmunology of coronavirus disease 2019 (COVID-19). *Rev Neurosci*. 2020;31(7):691–701.
  147. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect*. 2020;80(6):607–13.

148. Yeager A. Lost smell and taste hint COVID-19 can target the nervous system. *Scientist* 2020
149. Yoo J, Kim HS, Hwang DY. Stem cells as promising therapeutic options for neurological disorders. *J Cell Biochem*. 2013;114(4):743–53.
150. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng O-T, Marimuthu K, Ang LW, Mak TM. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA*. 2020;323(15):1488–94.
151. Zambrelli E, Canevini M, Gambini O, D'Agostino A. Delirium and sleep disturbances in COVID-19: a possible role for melatonin in hospitalized patients? *Sleep Med*. 2020;70:111–111.
152. Zhang GL, Zhu ZH, Wang YZ. Neural stem cell transplantation therapy for brain ischemic stroke: review and perspectives. *World J Stem Cells*. 2019;11(10):817–30.
153. Zhang W, Du R-H, Li B, Zheng X-S, Yang X-L, Hu B, Wang Y-Y, Xiao G-F, Yan B, Shi Z-L. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerging microbes & infections*. 2020;9(1):386–9.
154. Zhao D, Yao F, Wang L, Zheng L, Gao Y, Ye J, Guo F, Zhao H, Gao R. A comparative study on the clinical features of coronavirus 2019 (COVID-19) pneumonia with other pneumonias. *Clin Infect Dis*. 2020;71(15):756–61.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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