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The correlation between risk factors of COVID-19 and nervous system damage: Pakistan based Analysis

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Abstract

Aims: This narrative review's main objectives are to give the idea thorough COVID-19 and neurological diseases overview as well as to request a significant attention to important research areas that are closely related to the topic.

Methodology: "Coronavirus SARS/ COVID-19/ SARS-CoV-2," "neurology," "mechanism," "neuroinvasion," "neuron damage," "myopathy," "neuromuscular," "central nervous system," and "CNS" were used to search Medline, PubMed, and Google Scholar**.**

Results: highlights a number of significant findings, some of which consist of the detection of SARS-CoV-2 genome RNA in the cerebrospinal fluid, a probability for immediate infection of the central nervous system, penetrating to the brain's cortex via the olfactory nerve, as well as the implication of the peripheral nervous system in neurological disorders that are associated with COVID-19. Pakistani studies that found substantial neurological adverse responses in 23% of COVID-19 participants, the most prevalent from them were headaches and insomnia.

Scientific Novelty: Provide a deep overview of previous researches in order to find the link between COVID-19 and neurological diseases.

Conclusion: The link between COVID-19 and nervous system symptoms development during the pandemic is supported by neurological manifestations, which in accordance with studies are addressing the cerebral involvement of SARS-CoV and MERS-CoV. It is probable that the presence of neurological disorders in COVID-19 instances may increase the probability of patients with symptoms connected to neuroscience receiving an inaccurate diagnosis. These neurological issues that have been reported highlight how vital it is to realise the link between the SARS-CoV-2 infection and neurological impairments, as well as its association with the severity of the disease and death. Healthcare establishments should educate customers about COVID-19's neurological issues and report adverse events. Media can spread these messages. Governments can support research to find methods of treatment, and trade systems can import foreign pharmaceuticals for best results.

Keywords: COVID-19; SARS-COV; neurological damage; Pakistan.

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Introduction

Coronavirus disease 2019/COVID-19, which was caused by an infection with coronavirus 2 associated with severe acute respiratory syndrome (SARS-CoV-2), first appeared in the Chinese city of Wuhan in December 2019 and quickly spread throughout the world. The virus made a significant impact on the health care industry, community relations, and the economy [1]. The World Health Organisation (WHO) estimates that as of September 1, 2020, there will be 25,327,098 documented cases of COVID-19 including 848,255 reported fatalities across 216 nations, regions, and territories. The "beta-coronaviruses/beta-CoVs" genus is most closely linked to the SARS-CoV-2. This genus is responsible for the majority of infections that affect the humans' respiratory system. The "Middle East Respiratory Syndrome Coronavirus" (MERS-CoV), the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and SARS-CoV-2 are all examples of human beta-CoVs. They have a spike (S) protein that they are able to infect the host cells, and their genome is a single-stranded, positive-sense RNA [2, 3]. They are surrounded by a protective membrane and have a membrane envelope.

COVID-19 is a complicated multi-system illness that affects all body systems, including the cardiovascular, the respiratory system, the digestive tract, and the blood systems, in addition to the immune and nervous systems [4-6]. SARS-CoV-2 predominantly invades the lungs and results in COVID-19. COVID-19 is a disease that leads to COVID-19. COVID-19 causes a mild to moderate form of disease in the majority infected patients. On the other hand, individuals with severe illness manifest a variety of symptoms, including breathing problems and pneumonia, in addition to multiple organ failure and septic shock [7, 8]. According to clinical evidence, in addition to typical symptoms of breathing, neurological symptoms have been observed, notably in COVID-19-hospitalised individuals who have severe or critical diseases [9, 10]. This is because neurological manifestations are more likely to occur in patients who are already sick. There have been reports of neurological problems linked with SARS-CoV-2, which is consistent with the patterns seen with other coronaviruses. These difficulties are often connected to the central nervous system as well as to the peripheral nervous system (CNS and PNS, respectively), but the fundamental mechanism that causes damages is not well identified [11, 12].

Along with respiratory discomfort, patients diagnosed with COVID-19 have also been found to exhibit neurological symptoms, particularly those who are in a critical or severe condition. While the fundamental mechanisms have not yet been fully understood, there is evidence to suggest that the virus might induce neurological disorders that can impact both the central nervous system and the peripheral nervous system. The appearance of COVID-19 has brought to light the significance of international collaboration and prompt action in containing pandemics and reducing the negative effects they have. It is believed that continued attempts to create effective therapies and vaccines will lead to favourable results for afflicted people. These efforts are now underway. The COVID-19 pandemic, which was caused by SARS-CoV-2, has had a significant effect on the health of people all over the world, as well as on their social interactions and the economy. In addition to the primary impact on the respiratory system, the virus is also capable of causing neurological symptoms; many of them are not yet completely understood. There is, however a reason to be optimistic about the possibility of improved outcomes and a return to a more standard manner of life due to ongoing research and development.

Research Problem

The connection of COVID-19 with the development of nervous system symptoms during the pandemic is accompanied by neurological manifestations, which are in accordance with findings concerning the cerebral involvement of SARS-CoV and MERS-CoV. It is possible that the existence of neurological problems in COVID-19 cases may enhance the chance of patients with symptoms related to neuroscience receiving an incorrect diagnosis [15, 32]. In addition to this, it has been hypothesised that the possible recurrence of SARS-CoV-2 may be connected to the virus's latent state in the CNS [49]. These neurological difficulties that have been documented underline the importance of understanding the link between the SARS-CoV-2 infection and neurological impairments, as well as its association with the severity of the disease and death.

Research Focus

The purpose of this study is to provide an in-depth analysis of the risk factors co-relating COVID-19 and nervous system damage.

Research Aim and Research Questions

Based on this narrative review, the purpose of the project is to present a consensus regarding the main lines of action related to assessment, intervention, and acclimatisation of the risk factors co-relating COVID-19 and nervous system damage among Pakistani population.

1. What is the co-relation between COVID-19 and nervous system damage?
2. Which risk factors are associated with neurological damage in COVID patients?

3. What are the healthcare requirements for support and diagnosis of the problem in Pakistan?

Research Methodology

General Background

The primary goals of a narrative review are to provide the author and reader with a full overview of the topic at hand, and to draw attention to key areas of research that have been undertaken on the subject. Narrative reviews are excellent tools for detecting flaws in a study as well as for improving and identifying new areas for investigation. A summary of narratives might be the initial step toward undertaking an in-depth, rigorous investigation of the data and arranging it all in an acceptable manner. It is vital to explain the approaches that will be used in the process of conducting a narrative synthesis at the protocol stage. This is because a synthesis of narratives will be employed in an evaluation to some extent, whether substantial or trivial.

The literature search was carried out by using a number of different databases (for example, Medline, PubMed, and Google Scholar) with a combination of broad search terms, such as "Coronavirus SARS/ COVID-19/ SARS-CoV-2", "neurology", "mechanism", "neuro-invasion", "neuron damage", "myopathy", "neuromuscular", "central nervous system", and "CNS."

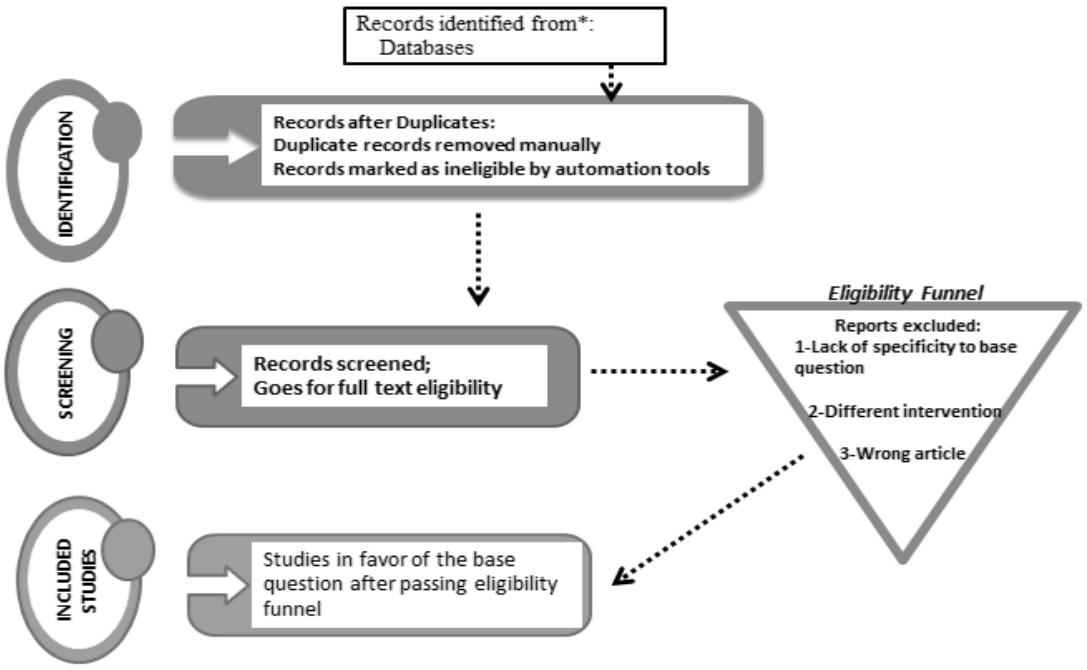

Figure 1. Graphical representation of extraction of information

Source: Author's own development

Data Analysis

The procedure for carrying out the analysis of the data started with the selection of the pertinent facts as the initial step of the process. The information that was gathered was first organised into a table, which was the second step in the process, which was followed by the drawing of conclusions about the study. After the articles that had been selected for further examination were reviewed one at a time, the overarching notion that most effectively demonstrates the relevance of the study issue was then determined.

Research Results

When the inclusion criteria were taken into consideration, a total of studies were found. (table 1). Nevertheless, in the perspective, there is a need for more concerned research that are randomised and controlled in order to determine the requirements of pregnant women and mothers and to give the appropriate treatment for their emotional discomfort.

Table 1. The extracted information from screened studies

Highlight of the review	Extracted information from Analysis	References
Direct Nervous System Infection	Detection of SARS-CoV-2 genome RNA in CSF of patients with COVID-19	[15, 27]
	aberrant cardiorespiratory center activity in the brain stem brought on by the neuro-invasive potential of SARS-CoV-2	[48]
	SARS-CoV-2 entry to the brain is possible, albeit infrequent	[49, 50]
	PNS offers easy entry points for this virus to the neurological system	[13, 51]
	SARS-CoV-2 could enter the brain via the olfactory nerve	[50]
	PNS parts, like neuromuscular junctions, might be involved in the neurological COVID-19 problem	[52, 53]
Possible Long-Term Neurological Effects of COVID-19	Chronic neuro inflammation brought on by SARS-CoV-2 will eventually result in neurodegenerative disorders.	[53, 54]
	Increased likelihood of neurodegeneration distinctive of this illness	
	COVID-19-associated storm of cytokines may work in concert to worsen cognitive deterioration in AD patients	[55]
	SARS-CoV2 infection may result in de novo neurological effects like PD by accelerated aging in the brain tissue	[56]
Pakistan based analysis	Pakistani study, 23% of volunteers who contracted the new coronavirus had significant neurological side effects	[57]
	Neurological problems are frequently noted in COVID-19 patients from Pakistan	[58]
	COVID-19based patients shows neurological symptoms are common	[58]
	headache and insomnia are most likely the neurological impairment felt	[58, 59]
	Measurement of psychological adaptability for maintaining quality of life	[38]

Source: Author's own development

This table provides a summary of the information that was retrieved from the studies that were examined on the neurological impact of COVID-19. It highlights several important findings, some of which include the identification of SARS-CoV-2 genome RNA in the cerebrospinal fluid, or CSF, of COVID-19 patients, the potential for direct infection of the nervous system and entry to the cerebral cortex via the olfactory nerve, and the significance of the peripheral nervous system (PNS) in neurological disorders associated with COVID-19. The table also shows that persistent neuro inflammation caused by COVID-19 may lead to neurodegenerative illnesses, and that COVID-19-associated cytokine storms can accelerate cognitive deterioration in patients with Alzheimer's disease. Both of these hypotheses are supported by the data presented in the table. In addition, the table shows a Pakistani study that identified substantial neurological adverse reactions in 23% of COVID-19 participants, with headache and insomnia being the most common symptoms. In conclusion, the table refers to a study that proposes assessing psychological adaptation in COVID-19 patients who are experiencing neurological symptoms in order to keep their quality of life from deteriorating. The last column contains the references that can be used to support the material that was extracted.

Discussion

Direct Nervous System Infection

The idea that the SARS-CoV-2 has infected the CNS has been supported by the evidence of cerebral participation in other CoVs (such as SARS-CoV and MERS-CoV) and the detection of SARS-CoV-2 genome RNA in CSF of patients with COVID-19 [15, 27]. Additionally, it has been proposed that individuals with COVID-19 may experience respiratory failure as a result of aberrant cardiorespiratory center activity in the brain stem brought on by the neuro-invasive potential of SARS-CoV-2 [48]. According to a recent study, COVID-19 patients' respiratory failure is distinct from that brought on by brain malfunction, albeit [49]. Due to the non-specific symptoms seen in COVID-19

patients, the SARS-CoV-2 entry to the brain is possible, albeit infrequent. Overall, SARS-CoV-2, like other CoVs, lacks sufficient evidence to support CNS entry, while it is hypothesised that previously established pathways for other infections may offer SARS-CoV-2 a route to the brain [49, 50]. One of the crucial channels for the entry of respiratory neurotropic viruses into the CNS is via neuronal retrograde paths [42]. In fact, the PNS offers easy entry points for this virus to the neurological system [13, 51]. Regarding this, it is conceivable that SARS-CoV-2 could enter the brain via the olfactory nerve. This notion is supported by the findings of an altered sense of smell (anosmia) [50]. Two crucial genes for SARS-CoV-2 invasion, ACE2 and TMPRSS2, did not express at olfactory neurons, according to bioinformatics analysis of mass and single-cell RNA-Seq records for SARS-CoV2 receptor gene expression at the system of olfactory receptors. Additionally, SARS-CoV-2-related proteins were found to be expressed in non-neuronal olfactory nerve cells, which are likely what causes anosmia after COVID-19 contamination, according to this study. However, additional PNS parts, like neuromuscular junctions, might be involved in the neurological COVID-19 problem. The concept that SARS-CoV-2 may attack the myelin or axon of muscle neurons is supported by elevated levels of CK and myalgia or weariness, which are seen in a sizeable percentage of hospitalisation COVID-19 patients [52, 53]. Evidence of other coronaviruses causing cerebral involvement as well as the finding of SARS-CoV-2 genome RNA in CSF both lend credence to the idea that SARS-CoV-2 could make its way into the central nervous system. However, there is not enough data supporting the idea that SARS-CoV-2 can enter the central nervous system. It is hypothesised that pre-existing routes in the brain that have been created for other infections may provide SARS-CoV-2 with a method to enter the brain. It's possible that the olfactory nerve is one of these pathways. A lack of a sense of smell is one of the symptoms of COVID-19, and proteins related to SARS-CoV-2 have been discovered to be produced in non-neuronal olfactory nerve cells. There is a possibility that neuromuscular connections are also implicated in the neurological issue caused by COVID-19. Elevated levels of CK and myalgia or fatigue are observed in a considerable percentage of hospitalised COVID-19 patients. These findings lend confidence to the hypothesis that SARS-CoV-2 may damage the myelin or axon of muscle neurons. In general, although there is not enough evidence to support SARS-CoV-2 entering the central nervous system (CNS), the virus may employ routes that have already been developed in order to enter the brain.

Possible Long-Term Neurological Effects of COVID-19

Insights into the involvement of the nervous system and signs of cognitive decline among COVID-19 patients are growing, and this information is troubling in that it points to potential delayed-onset neurological problems. Unexpected consequences of this illness could include worsening neurological problems that already existed or leading to a neurodegenerative condition in those who survived COVID-19. It is yet too soon to draw any firm conclusions about the probability that COVID-19 infection would have long-term neurological effects, but it is possible that chronic neuro inflammation brought on by SARS-CoV-2 will eventually result in neurodegenerative disorders. Additionally, the neuro-invasive properties of SARS-CoV-2 may lead to later neurodegenerative illnesses including multiple sclerosis (MS), Huntington's, Parkinson's, and Alzheimer's diseases (AD)[54]. The substantial likelihood of later neurological difficulties in COVID-19 survivors corresponds with other data showing that human CoVs can cause persistent CNS issues and latency in the nervous system. In other words, the chronic neuro inflammation as well as cytokine storm linked to COVID-19 severity, as well as the probable neuro-invasive aspect of SARS-CoV-2, highlight the potential increased likelihood of neurodegeneration distinctive of this illness [53]. The reports of COVID-19 infection in the CNS of individuals with PD, AD, and MS raise concerns regarding whether and how this neurodegenerative disease may be associated to COVID-19 infection [54]. For instance, the amyloid-stimulated interferon type I (IFN) response and the COVID-19-associated storm of cytokines may work in concert to worsen cognitive deterioration in AD patients. In AD patients who typically present with diarrhoea or tiredness due to COVID-19, it has been noted that significant systemic hypoxemia worsens the initial signs of dementia.[55] These varied clinical profiles may be related to various theories of age-related aetiology and how they affect individuals with pre-existing neurological disorders. SARS-CoV2 infection may result in de novo neurological effects like PD by accelerated aging in the brain tissue, which is a risk factor for both COVID-19 and neurodegenerative illnesses in older people [56]. There is mounting evidence that the nervous system is involved in COVID-19 individuals, including indicators of cognitive deterioration; this raises worries about the possibility of delayed-onset neurological issues. SARS-CoV-2 may raise the risk of developing neurological diseases because it causes persistent neuro inflammation and is neuro-invasive. Concerns have been raised regarding the possibility of correlations between COVID-19 infection and pre-existing neurological illnesses as a result of reports of COVID-19 infections in patients already suffering from these conditions. These varying clinical profiles may have a connection to the diverse hypotheses of age-related aetiology and how they affect people who already have neurological conditions. It is emphasises that it is still too early to draw solid conclusions regarding the long-term neurological effects of COVID-19, but stresses the probable increased probability of neurodegeneration that is characteristic of this illness.

Pakistan based Analysis

According to a recent Pakistani study, 23% of volunteers who contracted the new coronavirus had significant neurological side effects [57]. Despite the fact that these symptoms occur quite frequently, there hasn't been much research done on the subject in Asia [60]. After conducting a cross-sectional investigation Karachi, Makda A. et al. concluded that neurological problems are frequently noted in COVID-19 patients from Pakistan, accompanied with dizziness as the most prevalent symptom [58]. On the other hand, Kumar J. et al. pointed out that headache and insomnia are the most common neurological impairments. These inconsistent results highlight the need for additional research and make it challenging to address the symptoms that are already being experienced [58, 59]. From April to July 2020, a different cross-sectional study was carried out at a public tertiary care teaching hospital in Karachi, Pakistan. Except for those with pre-existing neurological and mental problems, every individual with positive polymerase chain reaction (PCR) tests were enrolled in the study. The outcomes revealed In terms of neurological symptoms, headache (such as 15.7%) and dizziness (such as 17.5%) were the most prevalent. Three individuals (such as 2.6%) experienced a stroke. A further nine (such as 7.8%) subjects had a smell impairment, while nine (such as 7.8%) participants had a taste impairment. When the incidence of neurological manifestations in patients with severe and non-severe form of disease was evaluated, there was no discernible difference. In COVID-19, neurological symptoms are common. It is important to spot them right away. To stop the spread of the virus, COVID-19 should be anticipated in individuals who present neurological problems and should be considered in the differential diagnosis [58]. It is alarming that a recent study conducted in Pakistan found a significant prevalence of neurological adverse effects in COVID-19 patients. This is especially true when one considers the rareness of research conducted on the subject in Asia. The findings imply that neurological symptoms, such as dizziness, headache, sleeplessness, stroke, and loss of senses of smell and taste, are common in COVID-19 in Pakistani. Particularly, the data suggest that COVID-19 patients in Pakistan are more likely to be male. Having these symptoms is not a prerequisite for having a severe illness; in fact, they can appear in people who have never experienced any neurological or mental complications in the past. The inconsistencies in the findings that were reported by various studies on the particular neurological symptoms that were encountered by COVID-19 patients indicate that additional research is required to better understand the effects that the virus has on the nervous system. It is very important to not only to treat the symptoms, but also to determine any potential long-term consequences on the nervous system. It is also vitally important to acknowledge the significance of quickly identifying neurological signs in COVID-19 patients. Because neurological symptoms can arise even in the absence of breathing problems, it is important to keep an eye out for COVID-19 infection if you experience any of these symptoms. This would make it possible to effectuate a fast diagnosis, isolate the patients, and treat them; all of this could help stop the virus from the further spreading. In addition, because COVID-19 may have possible long-term consequences on the nervous system, it is absolutely necessary to carry out additional study in order to gain a deeper comprehension of the mechanisms that are responsible for these neurological symptoms. This would be helpful in identifying potential therapies and techniques that may be used in order to minimise the neurological effects of the viral infection and prevent long-term consequences.

In this review, a variety of studies on COVID-19 effects on the nervous system are analysed. The finding that SARS-CoV-2, the virus that causes COVID-19, may directly infect the nerve system is one of the most significant. However, the virus is able to enter the body through the olfactory nerve and other locations in the peripheral nervous system (PNS). The ability of the virus to enter the brain is uncommon. This conclusion is backed up by a number of researches, including the ones described in references 13, 48, 49, 50, 51, and 52. In the review is also mentioned that COVID-19 may be responsible for chronic neuro inflammation, which may ultimately result in neurodegenerative illnesses; this hypothesis is provided in references 52 and 53. In addition, the analysis states that COVID-19-associated cytokine storms can accelerate cognitive decline in patients with Alzheimer's disease, and that SARS-CoV-2 infection may result in neurological sequelae such as Parkinson's disease. Both of these points are brought up in the review. One Pakistani study, cited as reference 56, found that 23% of COVID-19 patients' encountered significant neural side effects, while another reference, cited as 57, notes that neurological manifestations are often observed in COVID-19 individuals from Pakistan, with headache and insomnia being the most common symptoms. However, there is some dissonance in the prevalence and specific manifestations of neurological effects. One Pakistani study found that 23% of COVID-19 patients encountered significant neurological side effects. This review, in its entirety, offers a detailed study of current knowledge of the impact that COVID-19 has on the neurological system, drawing on a variety of resources to support its results.

Conclusions and Implications

This Research's findings concluded that:

1- The detection of SARS-CoV-2 genome RNA has been observed in CSF of patients with COVID-19.

2- Aberrant cardiorespiratory center activity in the brain stem brought on by the neuroinvasive potential of SARS-CoV-2.

3- The PNS offers easy entry points for this virus to the neurological system.

4- The SARS-CoV-2 could enter the brain via the olfactory nerve.

5- Chronic neuroinflammation caused by SARS-CoV-2 will eventually result in neurodegenerative disorders.

6- The SARS-CoV2 infection may result in de novo neurological effects like PD by accelerated aging in the brain tissue.

7- In Pakistan based study, 23% of volunteers who contracted the new coronavirus had significant neurological side effects.

8- Neurological problems are frequently noted in COVID-19 patients from Pakistan.

9- COVID-19based patients' neurological symptoms are common.

Author contributions

All authors have sufficiently contributed to the study and agreed with the results and conclusions.

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Ethical statement

This study does not require IRB approval as it does not involve human subjects/data.

Declaration of interest

No conflict of interest is declared by authors.

Data sharing statement

Data supporting the findings and conclusions are available upon request from the corresponding author.

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