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IMPACT OF COVID-19 ON MENTAL HEALTH: AN OVERVIEW

Virology

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ABSTRACT

A pandemic, according to the World Health Organization, is a widespread epidemic that affects a large number of people, spans across international boundaries, and occurs globally. Common initial symptoms of COVID-19 include fever, cough, fatigue, anorexia, and shortness of breath. However, the signs and symptoms can vary widely and affect different organ systems. Recent literature is starting to uncover the influence of COVID-19 on the nervous system and its neuropsychiatric consequences. The findings indicated a significantly higher rate of psychiatric disorders among patients recovering from COVID-19. Within 90 days post-diagnosis, there was a 5.8% probability of being newly diagnosed with a psychiatric illness. Anxiety disorders, particularly adjustment disorder, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and panic disorder, were the most frequently acquired diagnoses, with a 4.7% probability. Certainly, it is still debated whether psychosis is caused by COVID-19 or is a consequence of the drugs used for COVID-19 treatment (corticosteroids, antibiotics), internist conditions (hypoxemia, hydroelectrolyte imbalance), or related to stress due to long hospitalization or isolation. The findings of this review, while still debatable, show that COVID-19 stimulates psychotic symptoms in three main ways: direct action of the virus, deregulation of the cytokine network, and stressors and uncertainty related to prognosis disease. However, gaps still exist in this area and should be a place for further research. Nonetheless, this review suggests that future research should rigorously investigate the incidence of psychiatric symptoms in individuals with coronavirus infections, and a prospective cohort of SARS-CoV-2 patients should be formed.

KEYWORDS

COVID-19, Pandemic, Neurological manifestations

INTRODUCTION :-

A pandemic, according to the World Health Organization [1], is a widespread epidemic that affects a large number of people, spans across international boundaries, and occurs globally. Common initial symptoms of COVID-19 include fever, cough, fatigue, anorexia, and shortness of breath [2].

However, the signs and symptoms can vary widely and affect different organ systems. Recent literature is starting to uncover the influence of COVID-19 on the nervous system and its neuropsychiatric consequences. While large-scale cohort studies are currently lacking, a recent study explored the potential connection between COVID-19 and psychiatric disorders, revealing a reciprocal relationship [3].

The study involved 62,354 COVID-19 patients, examining the incidence and hazard ratios for psychiatric disorders, dementia, and insomnia within the first 14 to 90 days after a COVID-19 diagnosis.

The findings indicated a significantly higher rate of psychiatric disorders among patients recovering from COVID-19. Within 90 days post-diagnosis, there was a 5.8% probability of being newly diagnosed with a psychiatric illness. Anxiety disorders, particularly adjustment disorder, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and panic disorder, were the most frequently acquired diagnoses, with a 4.7% probability.

The probability of a new mood disorder diagnosis within 14 to 90 days after COVID-19 diagnosis was 2%. Notably, individuals with a pre-existing psychiatric illness had a 65% increased risk of being diagnosed with COVID-19 compared to a cohort without a psychiatric diagnosis but matched for established physical risk factors for COVID-19. This association remained consistent in sensitivity analyses.

Different Covid -19 Associated Neurological Manifestations:-

Delirium:-

In comparison to patients experiencing delirium due to other underlying health conditions, those with delirium in the context of COVID-19 have been reported to exhibit higher frequencies, increased mortality rates, more severe agitation, and a greater likelihood of presenting specific features like catatonia [4]. Various studies have reported delirium incidence in COVID-19 patients ranging from 30% to 50% [6–9]. Notably, one in five patients who succumbed to COVID-19 had encephalopathy [5]. The mortality rate in COVID-19 patients experiencing delirium has been documented as high as 55%, compared to 30% in those without delirium [6]. A study by Garcez and colleagues [6] utilized the Chart-based Delirium Identification Instrument (CHART-DEL) to identify delirium, revealing it as an independent predictor of in-hospital death. A case series from Massachusetts General Hospital highlighted that, beyond typical delirium features, COVID-19 patients exhibited notable agitation, increased tone or rigidity, abulia, alogia, and evidence of a significant systemic inflammatory response [7]. In a French case series involving 58 COVID-19 patients in the ICU, 26 tested positive on the Confusion Assessment Method for the Intensive Care Unit (CAMICU) scale. Agitation, corticospinal tract signs, and dysexecutive syndrome were observed in 40, 39, and 14 patients, respectively [8]. However, diagnostic accuracy in many of these studies appears limited, often relying on retrospective chart reviews or self-report questionnaires from patients [9]

Cognitive Deficits

Besides the heightened risk of altered mental status and delirium, there is emerging evidence indicating that COVID-19 can have an impact on cognitive functioning. This impact has been observed not only in patients without pre-existing cognitive impairment but also in those with a history of dementia. Previous studies examining the long-term neuropsychological outcomes in patients who required ventilation for medical conditions have revealed declines in various cognitive domains. These declines encompass impairments in memory, verbal fluency, processing speed, and executive functioning. Such cognitive deficits persisted in 78% of patients one year after discharge and in approximately half of the patients up to two years [10-12]. However, it remains unclear from the available information whether the patients in the study had experienced severe illness or not.

Psychosis:-

There are limited reports of new-onset psychosis in individuals with COVID-19 infection, and two main hypotheses have been proposed to explain this phenomenon: direct pathophysiological mechanisms and the impact of psychological stressors [13]. A UK study exploring neuropsychiatric symptoms in a COVID-19 database identified new-onset psychosis in 23 out of 125 patients meeting the clinical case definition for psychiatric diagnoses. Among these patients, 43% (10 out of 23) experienced new-onset psychosis [14]. However, the prevalence of psychosis observed in this study was not consistently reported in other studies, although there have been case reports and series addressing this issue. For instance, one case series highlighted

three COVID-19 patients who presented with new-onset psychotic symptoms despite being asymptomatic otherwise [15]. Several case reports document COVID-19 patients who initially manifested psychotic symptoms. These cases include individuals with positive SARS-CoV-2 test results and no previous psychiatric history presenting with psychosis [16], a COVID-19 patient experiencing command auditory hallucinations [17], and a case report describing heightened paranoia in a COVID-19 patient with a history of schizophrenia [18].

Depression:-

COVID-19 has been linked to elevated rates of depression in the general population [19], particularly among COVID-19 survivors [20]. Studies focusing on COVID-19 survivors reported depression prevalence ranging from 31% to 43% [20-22]. It's crucial to note that in these studies, depression assessment relied on self-rated questionnaires rather than clinical interviews, which are considered the gold standard for diagnosing major depression. Some research has delved into the biological mechanisms associated with depressive symptoms in COVID-19 patients. In a study involving 402 adult patients who underwent testing for various inflammatory markers during an Emergency Department visit for COVID-19-related symptoms, no significant correlation was found between inflammatory markers (Creactive protein, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and Systemic Immune-inflammation Index) and depression, except for a positive association between baseline Systemic Immune-inflammation Index and depression [20]. The Systemic Immune-inflammation Index reflects the balance between systemic inflammation and immune response, incorporating platelets, neutrophils, and lymphocytes.[23] Higher Systemic Immune-inflammation Index levels were previously associated with major depressive disorder [24]. Another study comparing various blood parameters in COVID-19 patients with and without self-reported depression found that white blood cell count, neutrophil count, neutrophil-to-lymphocyte ratio, and C-reactive protein levels were higher in the self-reported depression group [25]. Interestingly, a study by Guo and colleagues found no association between depressive symptoms and inflammatory indicators in the overall COVID-19 patient group [26]. However, it's essential to note that the patients in this study had mild illness, different inflammatory markers were measured compared to the study by Mazza and colleagues [20], and a control group was used for comparison. In patients with baseline depressive symptoms, C-reactive protein levels positively correlated with depression scores, while the change in C-reactive protein levels from baseline negatively correlated with depression scores, suggesting that an improved C-reactive protein level may result in fewer depressive symptoms.

Suicidal Ideation And Covid-19:-

Both clinicians and researchers have expressed concerns about the potential rise in suicidal ideation and suicide attempts as a consequence of COVID-19, drawing insights from studies conducted during previous pandemics and public health emergencies related to infectious diseases. A systematic review revealed increased suicide rates among older adults following the SARS outbreak, suggesting a link between SARS/Ebola exposure and heightened suicide attempts [27]. Various psychosocial complications associated with COVID-19, such as lockdowns, social distancing, isolation, loneliness, rising rates of depression, anxiety, substance use, domestic violence, limited access to health services, worsening physical illnesses, and the trauma of losing family and friends, are likely contributing factors. Additionally, misconceptions, fear, stigma related to COVID-19, and financial hardship due to job loss may play a role in elevating the risk of suicide [28]. A recent survey from the Centers for Disease Control and Prevention indicated a more than twofold increase in suicidal ideation among respondents in June 2020 compared to a similar survey in 2018. In this survey, 10.7% of 5412 adults reported serious consideration of suicide in the previous 30 days, whereas the 2018 survey reported 4.3% of 10.7 million adults with serious suicidal ideation in the previous 12 months [29]. However, it is yet to be determined whether COVID-19 has led to an actual increase in suicides. Studies conducted in Australia [30] and the USA [31] have not reported an increase in the number of suicides or suicidal behavior during the COVID-19 pandemic. Similarly, a recent systematic review by John and colleagues [32] did not reveal an increase in suicide rates or suicidal behavior during the COVID-19 pandemic. Two case reports from India and Bangladesh highlighted two suicides, attributing COVID-19-related stigma as a key driver [33,34]. Currently, no studies have systematically assessed the risk of suicide in COVID-19 survivors. A meta-analysis of studies investigating various psychiatric disorders in COVID-19 survivors did not identify suicide as a complication or manifestation [35].

Covid-19 Associated Mania:-

Several studies have established a connection between COVID-19 and depression, but there is a scarcity of data regarding the occurrence of mania in COVID-19 patients. Only a few reports [16, 36, 37] in the literature describe instances of mania following COVID-19 infection. Notably, in all these cases, individuals experienced mania for the first time in their lives, and they exhibited very few, if any, of the typical risk factors associated with mania. Additionally, the participants in these studies fell within the age range of 30s–50s, which is atypical for first-episode mania. A commonality among all these cases was the simultaneous onset of manic symptoms with ongoing COVID-19 symptoms.

Anxiety And Covid-19:-

COVID-19 has been associated with an increase in anxiety symptoms and anxiety disorders among both COVID-19 patients and the general population [19, 38, 39]. Furthermore, individuals with preexisting anxiety disorders who were not infected with COVID-19 were more adversely affected by the pandemic compared to those without a history of mental illness [40]. In a cross-sectional study involving 402 adults who survived COVID-19, the prevalence of PTSD, anxiety, and obsessivecompulsive symptoms was found to be 28%, 42%, and 20%, respectively [20]. Another study from China by Bo and colleagues reported a significantly high rate of posttraumatic stress symptoms among hospitalized COVID-19 patients, with 96.2% of 714 patients scoring above the threshold value on the posttraumatic stress disorder checklist-civilian version (PCL-CV) [41]. The psychosocial impact of the pandemic may contribute to an increase in anxiety and related disorders across various subgroups. This heightened risk encompasses the occurrence of new-onset disorders such as PTSD, GAD, panic disorder, and obsessive-compulsive disorder, particularly among vulnerable populations, as well as the exacerbation of these disorders in individuals already diagnosed. A recent systematic review by Pappa and colleagues highlighted a higher prevalence of anxiety disorders among healthcare workers [42].

Evidence Of Neuropsychiatric Manifestation Of The Drugs Used In The Treatment Of Covid-19

The healthcare community is confronted with a significant challenge in addressing the neuropsychiatric manifestations associated with COVID-19 infections. Immunomodulatory drugs, including hydroxychloroquine, ivermectin, remdesivir, systemic steroids, etc., have been linked to more severe symptoms such as delirium, psychosis, mood disturbances, and anxiety [43]. Notably, the pediatric population is more susceptible to developing these neuropsychiatric symptoms compared to adults [44]. National guidelines for managing COVID-19, tailored to symptom severity, recommend various treatments, including antipyretics like acetaminophen, antitussives, ivermectin, hydroxychloroquine/chloroquine, azithromycin, doxycycline, inhalational budesonide, methylprednisolone, dexamethasone, unfractionated heparin or low molecular weight heparin (UF/LMWH), remdesivir, tocilizumab, and convalescent plasma, among others[45]. However, due to ongoing changes in treatment guidelines and limited efficacy data, there is a concerning trend of inappropriate use of medications such as prednisolone, remdesivir, hydroxychloroquine, and immunomodulators, leading to an increased occurrence of neuropsychiatric adverse events among patients [46,47] . Unfortunately, these symptoms, especially those induced by medications, often go unnoticed, posing significant challenges in their management and contributing to higher morbidity and mortality rates [48]. Therefore, it is crucial for clinicians to be vigilant about these adverse events, understanding how to prevent, early detect, and effectively manage them [49].

Neuropathology Behind Covid-19 Neuropsychiatric Illness:-

The inflammation of the central nervous system as the cause of psychotic episode has been discussed by some authors[50,51].

Multiple pathways exist by which COVID-19 may cause mental health problems. Several infectious agents, such as HIV, Toxoplasma gondii, Treponema pallidum, Chlamydia trachomatis and Brucella, have been associated with psychosis [52,53]

The SARS-CoV-2 strain is neurotropic and potentially neurotoxic. [

50, 51]. To explain the neuropsychiatric symptoms of COVID-19 infection, two broad theories of central nervous system involvement have been postulated. Two factors contribute to the severity of COVID-19 disease: (1) direct viral invasion of the central nervous system: (a) through the olfactory bulb, through the cribriform plate and into the cerebrospinal fluid or the frontal lobe; or (b) through hematogenous dissemination across the blood-brain barrier.[54]. However, psychosocial stress from the pandemic has been associated with the worsening or onset of psychiatric disorders, regardless of the state of the infection [4].

Storm of cytokines is postulated as a second indirect method by which COVID-19 may generate psychosis. [55, 56, 57]. This mechanism arises from an aberrant immune response to this novel and unknown pathogen. When the immune system malfunctions, it creates a chain reaction that ultimately harms the brain tissue such as the excessive production of excitatory amino acids (glutamate). [55-57]. Such occurrences may damage neural pathways, increasing the risk of psychosis. These conclusions are supported by some authors who argue that SARS-CoV-2, either by direct neurotoxicity or by an exacerbated immunological response, could cause psychosis [55].

For example, SARS-CoV-2 RNA was recently extracted from a patient's brain, demonstrating that coronaviruses can spread to the neurological system [58].

Post-mortem studies of patients who died because of complications from COVID-19 have shown the presence of perivascular lymphocytic [59] infiltrates, microglia activation, microgliosis, and astrogliosis, evident signs of a neuroinflammatory process triggered by peripheral inflammation, or direct virus action in brain tissue [60]. The increase in permeability of the blood-brain barrier[61] caused by the ongoing cytokine storm associated with COVID-19 facilitates the entry of the virus into the SNC[60]. Brain tissue injury may express itself with an acute encephalitic pattern. Moreover, it is not excluded that Sars-CoV-2 may lead to long-term neuroinflammation with consequences in the same way as neurodegenerative diseases [62]. During COVID-19, the involvement of the olfactory epithelium with the subsequent anosmia, associated with an intense immune response, would be indicative of nerve tissue involvement and could therefore assume prognostic significance [62].

In summary, the neurotropism of SARS-CoV-2 and its clinical effects on the nervous system can be attributed to a combination of direct viral invasion, cytokine storms, molecular mimicry, and the consequences of systemic illness. Understanding these mechanisms is crucial for developing effective therapeutic strategies and interventions for individuals affected by neurological complications associated with COVID-1

Evidence Of Neurological Manifestations In Animal Of Post Covid-19 Condition:-

In GSH (Mesocricetus auratus), a valuable small animal model for studying SARS-CoV-2 infection, significant multi-organ damage has been observed, with inflammatory cell infiltration and necrosis in various organs. These include the upper and lower airways, secondary lymphoid organs, the digestive tract, kidneys, adrenal glands, and ovaries.[63, 64] The severity of lesions in non respiratory tissues remained mild, persisting up to 18 days post-infection (dpi). Viral genomic RNA and proteins were detectable in several organs up to 7 dpi, indicating a prolonged presence of the virus.

Studies on SARS-CoV-2-infected GSH revealed persistent pathological features in the brain, including microglial activation and accumulation of hyperphosphorylated tau and α-synuclein [65]. These features persisted even after viral clearance, contributing to long-lasting neurological signs without evidence of direct neuroinvasion. Comparison with influenza A virus (IAV) showed that SARS-CoV-2 induced more severe and longer-lasting histological alterations in the lungs and kidneys. Transcriptomic analysis revealed a unique profile in the olfactory tissue, suggesting potential neurobehavioral impacts. SARS-CoV-2-infected GSH exhibited changes in spontaneous rodent behavior, reduced burying activity, and prolonged mechanical hypersensitivity, resembling somatosensory abnormalities seen in patients with post-acute sequelae of SARS-CoV-2 infection.

The observed gray matter loss in limbic and olfactory cortical areas aligns with findings in human patients recovering from COVID-19. The transcriptomic analysis further highlighted the involvement of macrophages and Schwann cells in the SARS-CoV-2-induced proinflammatory state, contributing to persistent maladaptive neuronal responses even after viral clearance. These results emphasize the potential long-term neurological impacts of SARS-CoV-2 infection in this animal model.[66,67]

Given the significant differences in amino acid sequences between human and mouse ACE2, mice are not natural hosts for the ancestral SARS-CoV-2 strain due to the lack of functional receptor interaction [68]To overcome this limitation, researchers have employed various strategies, such as using hACE2-transgenic (hACE2-tg) mice with transient hACE2 expression and adapting the virus to the mouse environment.Several humanized mouse models have been developed to study post-acute sequelae of SARS-CoV-2 infection (PCC), particularly focusing on the respiratory tract [69] . MISTRG6 humanized mice, equipped with human immune cells and transient hACE2 expression, were used to mimic human immune responses. Results indicated that human immune cells contributed to lung inflammation and viral RNA persistence, possibly through direct infection of ACE2-expressing myeloid cells or phagocytosis of infected epithelial cells.Similar findings were observed in DRAGA humanized mice, which exhibit a functional human immune system and express hACE2 in the lung and upper respiratory airways. Lung pathology and inflammation persisted for up to 25 days post-infection [70].

In another model using AAV-hACE2 transduced wild-type CD1 mice, mild respiratory infection with no to moderate lung pathology was simulated. However, neuroinflammation was monitored up to 7 weeks post-infection, revealing increased levels of proinflammatory cytokines in both serum and cerebrospinal fluid (CSF). Notably, CSF levels of CCL11, associated with cognitive impairment, remained elevated, suggesting a potential link to neurological consequences [71].

DISCUSSION:-

The evidence regarding the increased occurrence of various neuropsychiatric disorders due to COVID-19 infection is still limited but is steadily growing. Given this, and drawing insights from studies during previous pandemics and infectious outbreaks, it's crucial to anticipate and screen for various neuropsychiatric symptoms among those diagnosed with COVID-19. It's important to note that individuals with preexisting neuropsychiatric disorders are more vulnerable to this infection and likely to experience a more severe course of the disease.

Reflecting on the 1918 Spanish flu pandemic, Karl Menninger presented cases associating mental disturbances with influenza. The follow-up study over five years revealed improvement in most patients with dementia praecox. Similarly, the HIV pandemic is known to significantly impact the brain, leading to various neurologic and psychiatric disorders. Several other viruses with limited geographic presence and variable transmission modes have been shown to cause neuropsychiatric symptoms, such as West Nile virus, enterovirus 71, Chikungunya, and Nipah.

Before the COVID-19 pandemic, coronaviruses caused notable outbreaks like severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012. A systematic review reported neuropsychiatric presentations in individuals with suspected or confirmed coronavirus infections. Psychosis was reported in a small percentage of patients with SARS during the acute stage.

Our review indicates a possible increased risk of delirium, cognitive impairment, psychosis, anxiety, and mood symptoms in patients with COVID-19. It's important to recognize the strengths of our paper in its timeliness and focus on elucidating biological mechanisms underlying neuropsychiatric symptoms due to COVID-19. However, it's crucial to acknowledge limitations, such as omitting non-English language papers and using a search strategy limited to the two most widely used search engines.

Mental health professionals are facing unique challenges during the acute phase of the pandemic, including caring for patients with serious mental illness and COVID-19, preventing infection spread in acute psychiatric units, and providing emergency mental health services. Telepsychiatry has become a new norm in the outpatient world,

transforming the practice of psychiatry over a short period.

CONCLUSION:-

In conclusion, this review has confirmed that the COVID-19 virus is associated with various psychotic symptoms, including hallucinations, delusions, disorganized behavior, and paranoia. Certainly, it is still debated whether psychosis is caused by COVID-19 or is a consequence of the drugs used for COVID-19 treatment (corticosteroids, antibiotics), internist conditions (hypoxemia, hydroelectrolyte imbalance), or related to stress due to long hospitalization or isolation. The findings of this review, while still debatable, show that COVID-19 stimulates psychotic symptoms in three main ways: direct action of the virus, deregulation of the cytokine network, and stressors and uncertainty related to prognosis disease. Many studies in this review indicate that COVID-19-induced psychotic symptoms are only short-lived and end within a few days of treatment. Furthermore, most studies agree that COVID-19 infection can cause early-onset psychosis and other psychotic symptoms, even among people without a history of mental illness, substance abuse, or medical condition. However, gaps still exist in this area and should be a place for further research. Nonetheless, this review suggests that future research should rigorously investigate the incidence of psychiatric symptoms in individuals with coronavirus infections, and a prospective cohort of SARS-CoV-2 patients should be formed.

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