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# Psychological Aspects of Neuroinflammatory Disorders in COVID-19 Era

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## Abstract

Although the COVID-19 pandemic was initially manifested as a contagious respiratory infection, its other aspects quickly became apparent. Accordingly, the disease could affect various organs such as skin, digestive system, and the central nervous system. Apart from these diverse manifestations, it was rapidly cleared that the virus could potentially play a role in causing a wide range of autoimmune diseases. Moreover, various anthropological aspects of COVID-19 and its effects on human life were considered. In this regard, one of the important issues is its psychological effects, not only on the population of healthy people, but also on people suffering from underlying diseases. Inflammatory diseases of the central nervous system are included as one group of these diseases. Since these diseases can cause many psychological problems in patients, it is very important to pay attention to them during the COVID-19 pandemic. In the following section, the psychological aspects of COVID-19 in patients with neuroinflammatory diseases are described.

**Keywords:** COVID-19, Psychological aspects, Neuroinflammatory disorders

## 1. Introduction

Since the start of the COVID-19 pandemic in December 2019, many different aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting pandemic conditions have been identified. Although COVID-19 was initially manifested as a lung disease as both pathogenic and lethal [1], it gradually became apparent that this disease can also involve other organs, including the central nervous system (CNS), [2] the peripheral nervous system [2], gastrointestinal tract [3], and skin [4]. These conflicts could be either due to the direct invasion of the virus or due to the response of the human immune system to it or the complications of both [2, 3]. Over time, of course, it became clear that the effects of the SARS-CoV-2 are not completely identified, and they are extended to a much wider range. By having a better understanding on the pathophysiology of this disease, our understanding on why it is so widespread could be improved. For example, scientists found that only a part of the symptoms were caused by the virus through directly invading tissues such as the lungs and nervous system, and most of the symptoms, leading to exacerbation of COVID-19 and even death, were due to the increased response of the human immune system to this virus. Correspondingly, the response is known as cytokine storm [5]. This enhanced immune response,

along with other mechanisms such as the similarity of virus proteins to human proteins, as well as the presence of genetic predisposing factors, have led to a wide range of autoimmune diseases following infecting with COVID-19 [6, 7]. Notably, some other problems can enhance the complexity of this pandemic. In the current research, the next topic is the psychological and psychiatric problems caused by the COVID-19 pandemic. These problems cover a wide range, all of which cannot only cause some problems in the patients' quality of life, but also have direct effects on various aspects of patients' life such as employment and education. On the other hand, these psychological aspects can be more reflected in someone with an underlying disease. Many of these diseases can be exacerbated by anxiety and depression; therefore, these people are more vulnerable to the psychological problems resulted from the COVID-19 pandemic. In the following section, we looked at these problems in people suffering from inflammatory diseases of the central nervous system. It was shown that these diseases, including multiple sclerosis (MS), are strongly influenced by stress, which in turn can exacerbate these diseases [8].

In this regard, a thorough understanding of the psychological aspects of COVID-19 and its consequences in this group of patients can help us in making better treatment decisions as well as discovering more effective prevention and counseling methods.

In this chapter, firstly, we examined the psychological effects of COVID-19 in general as well as the reasons of its occurrence, and then we studied those investigations specifically performed on these effects on patients with inflammatory diseases of the central nervous system. Finally, we mentioned the investigated methods to deal with these problems.

## **2. Psychological problems caused by COVID-19**

Since the start of the COVID-19 pandemic, numerous studies have been conducted on its psychological aspects. It was found that not only those developing COVID-19 are exposed to these psychological traumas, but fear of developing the disease and the economic and social conditions created by it also have increased the prevalence of these psychological traumas among all populations. Quarantine conditions that have limited human and social interactions, are known as important causes of these psychological traumas.

The conducted studies in this regard have focused on various aspects such as anxiety, depression, and stress. A study performed in Brazil on 3,000 people selected from 26 separate regions of the country, found that almost half of the participants suffered from some symptoms such as stress, anxiety, and depression [9]. Another study conducted on 1,879 people in the Philippines from March 28 to April 12, 2020, revealed that a quarter of their participants suffered from moderate to severe level of anxiety. Additionally, one in six of these people suffered from moderate to severe level of depression [10]. Another study reported a wide range of symptoms such as anxiety, depression, post traumatic stress disorder (PTSD), and the increased substance abuse [11]. As mentioned earlier, many of these people suffered from such injuries without developing COVID-19.

## **3. Causes of psychological problems in the COVID-19 pandemic**

Various causes manifested these psychological symptoms during the pandemic. Notably, developing COVID-19 was shown to increase the risk of psychological problems. A study performed on 402 patients recovered from COVID-19, found

that 28% of them suffered from PTSD, 31% suffered from depression, 42% suffered from anxiety, 20% suffered from obsessive compulsive symptoms, and 40% suffered from insomnia. This high rate of the occurrence of psychological disorders in people with COVID-19 indicates that the possible involvement of immune system leads to the development of these symptoms [12]. The same mechanism of the enhanced immune response occurring especially among severe cases of COVID-19 and then leading to various manifestations, has been implicated in causing such symptoms [12]. However, the pandemic itself, the fear resulted from it, and the socio-economic conditions that have arisen, regardless of whether a person is infected with this disease, are all involved in the occurrence of these psychological traumas.

Some people are at higher risk of such complications. In previous studies, various risk factors related to the possibility of psychological complications during the COVID-19 pandemic have been mentioned. For example, in a study conducted in the Philippines [10], some factors such as female gender, being unmarried, staying at home for a long time due to quarantine conditions, and poor health conditions were reported as effective factors on increasing the risk of psychological disorders in these people. In a systematic review, the factors exposing a person to psychiatric disorders were listed as follows: those who have developed COVID-19, people who were medical staff, elderly people or those with a previous history of Psychiatric disorders [13]. Another study emphasized that those who are medical staff or those caring patients are more exposed to various psychological injuries in pandemic conditions [14].

In addition to the above-mentioned general causes, psychological traumas in COVID-19 conditions can also have more specific reasons. As stated earlier, people with COVID-19 are prone to psychological traumas. One of the major causes of these injuries is the increased immune response during this disease, which is known as cytokine storm. This increased response can lead to a wide range of autoimmune diseases. These autoimmune diseases are not necessarily associated with brain involvement; however, they can cause a variety of psychological problems. Besides, autoimmune disorders of CNS following COVID-19, which are manifested in various forms such as MS [15], acute disseminated encephalomyelitis (ADEM) [16], and other demyelinating diseases [17], also have their own psychological symptoms [18].

On the other hand, by directly involving brain tissue, it was indicated that the SARS-CoV-2 can cause encephalitis, encephalopathy; and disorders associated with psychological manifestations such as memory impairment, hallucinations, and anxiety [19, 20].

The next important issue is the occurrence of COVID-19 in patients with neurological or those with psychiatric disorders. As mentioned earlier, a history of psychiatric disorder appears to increase the risk of exacerbating psychological symptoms during infecting with COVID-19. The same process should probably be true for neurological patients. It has been found that the presence of dementia increases the likelihood of exacerbation of COVID-19 [21], which may also increase the risk of psychological problems.

Inflammatory diseases of the brain include a wide range of diseases that can cause various manifestations such as cognitive and psychological ones. Given the above-mentioned reason, it is likely that these patients are more prone to psychological traumas due to various factors occurring during the COVID-19 pandemic. In the following section, we examined various psychological aspects of patients with inflammatory brain diseases during the COVID-19 pandemic and concluded some therapeutic recommendations for providing further services to these patients.



## **4. Psychological aspects of neuroinflammatory diseases under COVID-19 conditions**

Neuroinflammatory diseases include a wide range of diseases that can be divided into two general groups. Accordingly, the first group includes diseases such as MS, neuromyelitis optica spectrum disorder (NMOSD) or cerebral vasculitis, which are known with the ability of involving the CNS. The second category includes a wide range of systemic diseases such as rheumatic or infectious diseases, which can also involve the CNS.

### **4.1 MS**

MS is an autoimmune disease of the central nervous system that can cause a wide range of symptoms. The incidence and prevalence rates of this disease are increasing day by day and it mainly affects the young generation aged between 20 and 40 years old [22]. MS is known as one of the leading disease of the central nervous system that can have many effects on individuals' life and their social relationship. The range of symptoms occurring in this disease is wide, which varies from numbness, paresthesia, visual impairment, movement problems, and urinary problems to cognitive and psychological disorders [23]. Moreover, this disease causes a range of psychological disorders in the affected patients. The most common psychological illness associated with MS is depression; however, other psychological disorders such as anxiety, emotional intelligence problems, bipolar disorder, and psychosis were also found to be related to this disease [24, 25].

As the disease progresses, both the type and prevalence of these psychological disorders can change. Additionally, the personality of the patients can change, which could be due to the effects of the disease, the resulted cognitive impairment, and the effects of medications [26].

These psychological disorders cannot only affect the severity of the disease, but they can also affect the patients' desire to pursue treatment. Therefore, these disorders' treatment is very important [27].

Many of these psychological manifestations mostly have an internal aspect and are caused by the pathology of the CNS as well as the involvement of the relevant areas by the same autoimmune mechanism that has led to the disease and its symptoms [28].

It was expected that such a disease with this magnitude and complexity could be affected in various ways in the COVID-19 pandemic. All the mechanisms mentioned earlier about the causes of psychological disorders in COVID-19 conditions were also found to affect MS patients. Accordingly, the studies that have been done in this regard also showed these broad dimensions.

#### *4.1.1 Psychological aspects of MS during the COVID-19 pandemic*

Numerous studies have examined various psychological aspects of patients with MS during the COVID-19 pandemic. From the very beginning of this pandemic, the psychological effects of COVID-19 on patients with MS have been noticed. In this regard, in a study conducted at the beginning of the pandemic, it was found that the level of anxiety is moderate to high in these patients [29]. However, this study was performed on a limited number of patients with no control group.

Another larger study found that MS patients suffered from more anxiety and depression during the COVID-19 pandemic compared to healthy individuals and their caregivers [30]. This high anxiety was not only due to the previously discussed general condition of COVID-19, but the patients with MS also had other concerns.

Accordingly, they were concerned about the worsening of their disease following COVID-19 and also about the possible impact of the condition resulted from this pandemic on the availability of their main drugs. They also expressed their concern that they might not be able to receive the required hospital services to treat their MS under the above-mentioned condition [31, 32].

Another study found that people with MS have become more sad and anxious during this pandemic, which is in line with previous studies. The fact that their treatment visits were delayed due to pandemic conditions and the concern about not receiving their medications on time were the reasons for this worriedness, as 40% of the patients participated in this study requested for psychological services during this pandemic [33]. In fact, it seems that MS patients are more concerned about the worsening of their disease during the COVID-19 pandemic than the consequences resulted from developing COVID-19 [34].

Notably, some other studies have also reported the neuropsychiatric effects of the COVID-19 pandemic on people with MS. According to the estimations, the rate of depression during the COVID-19 period has increased in these patients, and this pandemic had a direct impact on the quality of life in these patients [35]. In a study conducted on 432 patients, it was found that 31.7% of patients suffered from significant PTSD-like symptoms. Moreover, 48.6% of patients suffered from moderate-to-severe anxiety, 22% suffered from moderate-to-severe depression, 50.9% suffered from moderate-to-severe stress, and 29.6% of patients suffered from insomnia [36].

Various causes were found to be involved in causing psychological problems in MS patients during the pandemic. Apart from the above-mentioned reasons about the reduced access to physicians and appropriate services, younger age, more severe degree of MS, low adaptability, less optimism, more loneliness, and less resilience have also been found to be associated with higher rates of depression [37].

Despite all these findings, due to the increasing prevalence of this disease worldwide, further studies are needed on the psychological effects of COVID-19 pandemic on MS patients. These patients due to their underlying disease suffer from a number of neuropsychiatric disorders [38] that increase the risk of being affected under critical condition such as a pandemic. High levels of depression, anxiety, adjustment disorders, emotional intelligence problems, and cognitive impairments all can increase the likelihood of these negative effects as well as their subsequent consequences. Therefore, these patients require paying special attention under such conditions [38].

#### **4.2 Psychological aspects of NMOSD during the COVID-19 pandemic**

NMOSD is an inflammatory disease of the central nervous system mainly characterized by the involvement of the optic nerve and spinal cord. Unlike MS, it is an astrocytopathy that can cause many physical problems with its disabling attacks [39]. Moreover, while MS is a relatively high prevalent disease, NMOSD is a rare disease with a prevalence ranged from 0.51 to 4.4 per 100,000 [40]. Therefore, it is clear that unlike MS, many aspects of NMOSD are unknown yet. However, our understanding on the disease, especially after the discovery of the aquaporin 4 antibody, has greatly increased and it became clear that this disease can have a wide range of manifestations. Of note, central nervous system involvement in this disease is not limited to the optic nerve and spinal cord and it can be associated with involvement of the brain parenchyma [41]. In recent years, some studies have reported cognitive impairment in NMOSD patients, which may reflect the brain involvement in these patients. In a systematic review, the rate of cognitive impairment in these patients was reported as 44% [42]. In addition, in

a few studies conducted on psychological disorders in patients with this disease, it has been shown that psychological problems are significantly prevalent in these patients. Ebadi et al. in their study found that depression, anxiety, hostility, and somatization rates were significantly higher in NMOSD patients compared to the control group [43]. Other studies have reported high rates of depression in these patients [44, 45]. It should be noted that the presence of brain involvement as well as psychological disorders in these patients can expose them to psychological damage during the COVID-19 pandemic. In addition to these, the type of drugs used, which are mainly immunosuppressive drugs, can increase anxiety due to fear of developing COVID-19. Furthermore, in a study by Sahraian et al., it was found that rituximab, which is one of the main drugs used in the treatment of this disease, can increase the chances and severity of COVID-19 disease in these patients [46]. This issue can be considered as a basis for psychological trauma in these patients during the pandemic of COVID-19. Correspondingly, in a study conducted by Shaygannejad et al., this issue has been mentioned as a cause of concern in these patients [47].

Despite all these facts, unfortunately, no study has been done on the psychological effects of the COVID-19 pandemic in patients with NMOSD yet. However, due to the above-mentioned reasons, these patients are highly at risk of psychological damage during a pandemic. In this regard, in addition to the requirement of performing studies on this issue, psychological treatment recommendations should also be considered for these patients during a pandemic.

#### **4.3 Psychological aspects of other neuroinflammatory diseases during the COVID-19 pandemic**

As far as the author of this study is concerned, with the exception of MS, a few studies have been done on the psychological aspects of other inflammatory diseases of the brain like NMOSD. This is also true for other neuroinflammatory diseases, especially those that involve the CNS in a secondary way. For example, up to now, there have been no studies on the psychological aspects of diseases such as neuroinfectious diseases, neurosarcoidosis, or other similar ones. The reason can be attributed to the low number of these cases. However, several studies have been conducted on the psychological aspects of diseases that can potentially lead to inflammatory involvement of the CNS, which also indicated the psychological effects of a pandemic on these patients. A study conducted three months after the onset of the pandemic in the Philippines reported that patients with lupus and rheumatoid arthritis are suffering from a significant proportion of psychological problems. According to this study, 38.7% and 27% of these patients suffered from moderate to severe anxiety and depression, respectively [48].

A study showed a high rate of depression as well as the increased risk of suicide in patients with rheumatoid arthritis during COVID-19 pandemic [49]. Another study on 134 patients with lupus also found that the depression, anxiety, and sleep disorders rates in patients with lupus were higher than those of the normal population during the pandemic [50].

Another systemic disease that can be found in association with known inflammatory manifestations of the central nervous system is Behçet disease. Unfortunately, like other similar cases, the effects of the COVID-19 pandemic on patients with Neuro-Behcet Disease (NBD) have not been well-studied yet. However, a study on 156 patients with Behcet's disease revealed that these patients are also suffering from more anxiety and depression than the control group and are more prone to suicidal ideation [51], emphasizing on the need for more psychological care.



#### **4.4 COVID-19 and autoimmune encephalitis**

Although autoimmune encephalitis is included in a very broad category, it is still a rare disease. Therefore, it is not far-fetched if a study has not been conducted on the psychological effects of COVID-19 on this disease so far. However, there is a very important point about these diseases that should be considered, which is as follows: Neuropsychiatric manifestations including cognitive impairment, psychosis, and depression are considered as common themes in autoimmune encephalitis, which can even be early manifestations of the diseases [52]. Therefore, according to previous studies, these patients are more prone to psychological injuries caused by COVID-19 compared to the healthy people. Another important point is that COVID-19 can be known as a factor in the development of autoimmune encephalitis. There are reports on autoimmune encephalitis cases following COVID-19 [53, 54]. On this regard, Panariello et al. reported a 23-year-old man hospitalized with some symptoms such as delusion, anger, anxiety, and auditory hallucination. Due to the presence of fever in his examinations, the patient was diagnosed with COVID-19. Following the deterioration of the patient's neurological condition, further examinations were performed and the patient's Anti-N-methyl-d-aspartate receptor (NMDAR) test was also resulted as positive. Therefore, he was treated with Intravenous immunoglobulin (IVIG) and his condition has then improved [53]. In fact, COVID-19, as a factor effective on developing autoimmune encephalitis, can present itself through psychiatric manifestations.

### **5. Treatment**

As mentioned earlier, people with inflammatory brain diseases can be severely affected by various aspects of the pandemic and then experience a variety of psychological injuries. Therefore, paying enough attention to various points in preventing the occurrence of these psychological injuries and treating them can help in improving these patients' condition.

#### **5.1 Diagnostic recommendations**

The first point in the treatment is paying special attention to the psychological disorders caused by COVID-19 in patients with neuroinflammatory diseases. It should be noted that most of the aspects of these psychological injuries have not been identified yet. As mentioned previously, since a large number of these diseases are considered as rare diseases, so no study has been done on them so far. Therefore, besides paying special attention to these symptoms and trying to improve them, various studies should be continuously conducted on them, only then we can provide better services to these patients. On the other hand, most of these diseases were found to be associated with psychological disorders. Differentiating the conditions caused by COVID-19 from those of the psychiatric disorders caused by the disease itself can help us in providing better treatments and services.

#### **5.2 Psychological recommendations**

Various factors were reported to be involved in causing psychological injuries in patients with neuroinflammatory diseases during the COVID-19 pandemic. Accordingly, one of them is the fear of developing COVID-19 and the complications resulted from that. Providing health advice to prevent infection can help in improving the mental condition of these patients. Moreover, these patients should be advised to take such pieces of advice carefully and then follow them regularly.



The use of online methods and telemedicine can also help in reducing the anxiety of these patients as well as preventing them from being present in places where there is a possibility of disease's transmission. Online psychological services can also help patients to express their problems, and consequently reducing their psychological problems [55, 56]. Unfortunately, this service has not been prepared for patients with neuroinflammatory diseases and a special model for online interview doesn't exist. However, some important points should be considered:

Depression, anxiety and PTSD are the most important issues in this interview and mental health professionals should emphasize on these symptoms. In addition, they should know the medical aspects of neuroinflammatory diseases and patients' concerns about their condition during COVID-19 pandemic. This knowledge helps therapists to do better interviews with these patients.

### **5.3 Physical activity**

Advising to continue physical activity under pandemic conditions can help in reducing patients' psychological problems. Quarantine conditions as well as social distancing cause these patients to stay home more often and to avoid physical activities [57].

A study performed on patients with rheumatoid arthritis found that physical activity could significantly reduce the mental health problems among these patients. Physical activity was also found to be associated with the decreased depression and the increased vitality [58]. It is important to pay enough attention to various aspects of these patients' problems such as cognitive, gastrointestinal, and motor problems, and then to notice these symptoms and the possibility of their exacerbation during the COVID-19 pandemic. Developing rehabilitation programs for these patients with varying degrees of disability can also be effective on improving their mental health. Using cyberspace and holding online rehabilitation programs can help in reducing patients' problems and then reducing the anxiety of developing Covid-19 as it may happen by participating in face-to-face rehabilitation programs [59].

### **5.4 The role of special associations in reducing the possible problems of the patients during the time of COVID-19**

Up to the author's knowledge, most of the psychological aspects have not been studied in a wide range of specific patients yet, and research remains practically limited only to a few diseases. The roles of associations in providing regular programs and psychological, physical, and therapeutic advices to these patients are of great importance. Many of these patients also need receiving psychological support from medical staff. Such a communication can be on the agenda of the relevant associations.

## **6. Conclusion**

Neuroinflammatory diseases are prone to different psychological problems during the COVID-19 pandemic. It is very important to pay attention to them and manage these complications carefully.

### **Conflict of interest**

The author declares there is no conflict of interest.

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