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**RESEARCH ARTICLE**

## Immunotherapy for Post-COVID Neuropsychiatric Symptoms: The Potential of IVIG Treatment

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**ABSTRACT**

This paper explores the neuropsychiatric consequences of SARS-CoV-2 (COVID-19) infection, specifically the use of intravenous immunoglobulin (IVIG) therapy in treating central nervous system (CNS) symptoms associated with COVID-19. The authors searched PubMed and Google Scholar using the keywords "IVIG" and "covid-19 neuropsychiatric symptoms" to find five articles, including three case reports, a retrospective study, and a prospective study, that detail the experiences of individuals with persistent neuropsychiatric symptoms after contracting COVID-19. The neuropsychiatric symptoms reported in the analyzed studies include sleep disturbance, exhaustion, cognitive decline, anxiety, and others. Common treatments for post-COVID neuropsychiatric symptoms include medications, cognitive behavioral therapy, and lifestyle modifications. IVIG therapy to manage CNS symptoms of COVID-19 has shown mixed results in studies, with some showing positive effects while others remain inconclusive. Further research is needed to understand this therapy's potential benefits and limitations fully.

**KEYWORDS**

Immunotherapy, Post-COVID, Neuropsychiatric symptoms, IVIG treatment, COVID-19, Autoimmune disorders, Psychiatric disorders, Neuroinflammation, Immune system, Antibodies

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**1. Introduction**

Individuals who have been infected with the SARS-CoV-2 virus (COVID-19) may experience various neurological symptoms post-infection, sometimes known as "Long COVID" [Calabria, 2022]. The most common of these symptoms is sleep disturbance, followed by feelings of exhaustion and measurable cognitive decline. Other common symptoms include anxiety and post-traumatic stress disorder (PTSD). It is important to note that these symptoms can vary greatly in their severity, duration, and onset after infection [Calabria, 2022, Badenoch, 2022]. Despite the widespread psychological distress caused by COVID-19 and the pandemic, our understanding of how the virus and the host's immune response can affect the human central nervous system and result in neuropsychiatric consequences remains limited. The relationship between the virus, the immune response, and its effects on the human brain and mental health are yet to be fully understood [Troyer, 2020].

The treatment approach for individuals with post-COVID neuropsychiatric symptoms will vary based on their specific symptoms and severity. Common treatments include antidepressants or anxiolytics to manage depression and anxiety [Tang, 2022]. Cognitive behavioral therapy (CBT) may help individuals cope with symptoms and address related psychological distress [Sacks-Zimmerman, 2023]. In addition to these specific treatments, lifestyle modifications, such as regular exercise and physical activity, can also contribute to managing post-COVID neuropsychiatric symptoms. Research has shown that these lifestyle changes can enhance cognitive functions such as attention, processing speed, executive functioning, and memory in affected individuals [Rolin, 2022].

The use of intravenous immunoglobulin (IVIG) to treat neuropsychiatric symptoms after COVID-19 infection is still a new and developing field of study. While there is some evidence suggesting that IVIG may be effective in treating certain neuropsychiatric symptoms in some patients, much is still unknown about its use for this purpose [Muccioli, 2021]. The use of IVIG to treat neuropsychiatric symptoms after COVID-19 infection presents several knowledge gaps that require further research. One of the main issues is the efficacy of this treatment, which has not been conclusively established. Additionally, the mechanisms by which IVIG may be effective in treating these symptoms are not well understood. Patient selection is also a challenge as it is not clear which patients are most likely to benefit. Furthermore, the long-term safety of IVIG for this purpose has not been well established, and further research is needed to identify potential side effects or adverse events associated with its use.

Intravenous immunoglobulin (IVIG) therapy involves the administration of antibodies through an intravenous injection. The therapy effectively treats some symptoms of systemic COVID-19, which refers to the widespread effects of the virus throughout the body. However, the specific role of IVIG therapy in treating central nervous system (CNS) symptoms associated with COVID-19 remains unclear [Muccioli, 2021].

While there is some evidence to suggest that IVIG may be effective in treating neuropsychiatric symptoms after COVID-19 infection, much remains unknown about this treatment approach. Further research is needed to fill these knowledge gaps and to determine the best way to use IVIG to treat these symptoms in patients. This study seeks to determine IVIG therapy's potential benefits and limitations in managing CNS symptoms of COVID-19.

**2. Methodology**

**2.1 Search Strategy**

The search was conducted using the databases PubMed and Google Scholar, with keywords "IVIG" and "covid-19 neuropsychiatric symptoms" combined using the Boolean operator "AND" to generate a list of articles.

**2.2 Inclusion and Exclusion Criteria**

The papers were screened based on pre-defined criteria: relevant to the research topic, published and peer-reviewed, in English or with English translation, published within the last five years, and full-text access. Papers that did not meet these criteria, review articles, gray literature, and irrelevant papers were excluded.

**3. Results and Findings**

A search was conducted on February 2nd, 2023, using the Google Scholar database and PubMed. The Google Scholar search produced 43 articles, which were narrowed down to 33 after applying filters. The PubMed search generated six articles, with five remaining after filtering and removing one duplicate. The selected articles underwent title and abstract screening to assess their relevance, resulting in five articles being chosen for inclusion. In cases of dispute, when determining the eligibility of articles, the co-authors worked together to reach a unified decision on which papers would be included. All full texts were accessible.

**Table 1: Search Results Using Databases**

Database	Initial Results	After filters	Included
Google Scholar	43	33	3
PubMed/MEDLINE/PMC	6	5	2
Total	49	38	5

**Table 2: Articles Chosen for Inclusion**

Author, Year	Study Type	Participants
Della Corte et al., 2022 [Della Corte, 2022]	Case report	1
Efe, 2022 [Efe, 2022]	Case report	2
Muccioli et al., 2021 [Muccioli, 2021]	Observational	5
O'Leary et al., 2021 [O'Leary, 2021]	Case report	5
Zahed et al., 2022 [Zahed, 2022]	Observational	58*

\* Study included 375 patients, of which 58 had psychiatric symptoms

#### 4. Discussion

The COVID-19 pandemic has caused a global health crisis and brought to light the many challenges healthcare professionals face in treating the long-term effects of the virus [Troyer, 2020]. One of the most significant and persistent challenges is the management of the neuropsychiatric effects of COVID-19 [Cothran, 2020]. Individuals who have contracted the virus have reported significant and lasting alterations in their neuropsychiatric symptoms, making it difficult for healthcare providers to treat them effectively [Calabria, 2022]. This highlights the need for treatments that target the immune response triggered by the virus, which is believed to be the root cause of these persistent neuropsychiatric effects [Troyer, 2020]. These cases underline the importance of continued research and development of treatments that can help alleviate the long-term neuropsychiatric symptoms of COVID-19 and improve the quality of life of those affected by the virus.

Our literature review produced five articles, including three case reports, a retrospective study, and a prospective study. These studies detail the experiences of populations with varying characteristics which have suffered from persistent neuropsychiatric symptoms after contracting COVID-19. The number of participants in each study varied, with the smallest study having one participant and the largest having 58 participants (who were affected with psychiatric symptoms).

##### 4.1 Neuropsychiatric Symptoms

The neuropsychiatric symptoms reported in the analyzed studies were varied and diverse. Some patients reported sudden onset symptoms, including severe restriction in food intake and obsessive-compulsive behavior [Efe, 2022]. Other individuals reported symptoms such as confusion, fluctuating mood, impulsiveness, agitation, and rapid speech [O'Leary, 2021]. There were also cases of subacute onset of positive and negative limb and facial myoclonus, drowsiness, and memory impairment [Della Corte, 2022]. In addition, some patients experienced symptoms such as irritability, confusion, disorientation, apraxia, decreased level of consciousness, and agitation [Muccioli, 2021]. In the study by Zahed et al., 58 patients were found to be exhibiting psychiatric manifestations of Seasonal Affective Disorder (SAD), Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), insomnia, Oppositional defiant disorder (ODD), phobias, and Obsessive-compulsive disorder (OCD), with their corresponding symptomatology. The participants were tested for psychiatric symptoms at the end of their first month of COVID-19 manifestations, and it is unclear whether these participants had pre-existing psychiatric conditions or if these were new diagnoses [Zahed, 2022].

Post-COVID neuropsychiatric symptoms can persist for weeks, months, or longer after recovering from COVID-19. These symptoms include fatigue, cognitive impairment, mood changes, headaches, dizziness and vertigo, neuropathic pain, and, in rare cases, psychotic symptoms. The severity and duration of these symptoms can vary among individuals, and other less common symptoms may also occur [Nakamura, 2021].

**Table 3: Symptoms Reported in the Studies**

Author, Year	Symptoms
Della Corte et al., 2022 [Della Corte, 2022]	Subacute development of myoclonus, drowsiness, and memory deficits
Efe, 2022 [Efe, 2022]	Acute onset, severe and restrictive food intake, and obsessive-compulsive disorder
Muccioli et al., 2021 [Muccioli, 2021]	Irritability, confusion, disorientation, apraxia, decreased level of consciousness, agitation
O'Leary et al., 2021 [O'Leary, 2021]	Confusion, labile mood, impulsive, agitation, pressured speech
Zahed et al., 2022 [Zahed, 2022]	Psychiatric disorders including SAD, MDD GAD, insomnia, ODD, specific phobia and OCD

##### 4.2 Treatments and Use of Intravenous Immunoglobulins

Treatment options for post-COVID neuropsychiatric symptoms vary depending on the symptoms and underlying causes. Common approaches include medication, cognitive and behavioral therapies, physical therapy and rehabilitation, supportive care, and intravenous immunoglobulin (IVIG) [Benzakour, 2022]. Supportive care and education may be sufficient for mild or moderate symptoms, while IVIG is a potential treatment option, but its efficacy needs more research [Muccioli, 2021]. Antidepressants, anti-anxiety medications, and antipsychotics may be used to treat specific symptoms, while psychotherapy, such as cognitive-behavioral therapy (CBT), can help manage and overcome anxiety or depression [Benzakour, 2022]. Physical therapy and rehabilitation can improve function and independence for those with physical symptoms [Benzakour, 2022].

It's important to note that the most effective treatment for post-COVID neuropsychiatric symptoms will depend on the individual patient and the specific symptoms they are experiencing [Benzakour, 2022].

The studies reviewed in this analysis highlight the varied approaches to treatment for patients with neuropsychiatric symptoms. Despite the differences in treatment strategies, intravenous immunoglobulin (IVIG) was a common component in all studies. The timing of IVIG administration and its effectiveness in achieving positive outcomes are crucial factors that require further examination.

**Table 4: Treatments Administered in Each Study**

<b>Author, Year</b>	<b>Treatments Administered</b>
Della Corte et al., 2022 [Della Corte, 2022]	Clonazepam initially improved the patient's generalized myoclonus, but it was later substituted with intravenous methylprednisolone for five days, followed by a prednisone taper. As the patient showed a poor response, a five-day cycle of IVIG (0.4 g/kg/day) was administered, resulting in a gradual reduction of involuntary movements and an improvement in cognitive performance.
Efe, 2022 [Efe, 2022]	Both sisters received psychotropic and antibiotic treatments, including amoxicillin-clavulanate for 21 days. The more affected sister was prescribed fluoxetine, risperidone, and sodium valproate, while the less affected sister received sertraline. However, after one month, despite some improvement, the severe symptoms persisted and an IVIG transfusion was administered.
Muccioli et al., 2021 [Muccioli, 2021]	Treatment involved the administration of IVIG at a dose of 0.4 g/kg/day began on average 29.8 days (with a range of 19-55 days) after the onset of encephalopathy.
O'Leary et al., 2021 [O'Leary, 2021]	The patient was initially given a low dose of haloperidol, which was gradually increased and supplemented with trazodone. Later, quetiapine replaced haloperidol. On the tenth week of admission, the patient was treated with 20 g of IVIG for five consecutive days. However, 16 weeks after the initial presentation, the patient's cognitive and psychiatric condition deteriorated, and a video EEG showed bi-frontal periodic epileptiform discharges. The patient showed improvement with the use of anti-epileptic drugs, specifically levetiracetam and clobazam.
Zahed et al., 2022 [Zahed, 2022]	The most frequently received treatment was corticosteroids, followed by antivirals, intravenous immune globulin IVIG, anti-malarial drugs, antiepileptic drugs, and others.

**4.3 Mechanism of Action**

The exact mechanism by which intravenous immunoglobulin (IVIG) may treat post-COVID neuropsychiatric symptoms is not well understood. However, there are several potential explanations based on the known actions of IVIG.

IVIG is a collection of antibodies obtained from the plasma of thousands of healthy donors [Pourahmad, 2020]. When administered intravenously, IVIG can help boost the immune system and provide a rapid and broad-spectrum antibody response [Pourahmad, 2020]. In the context of COVID-19, it's thought that the antibodies present in IVIG may help neutralize the virus and reduce inflammation in the body, including the brain [Pourahmad, 2020].

Additionally, IVIG has been shown to have immunomodulatory effects, meaning that it can help regulate the immune system and reduce excessive or persistent inflammation [Pourahmad, 2020]. This may be particularly relevant in the context of post-COVID neuropsychiatric symptoms, which have been linked to inflammation and immune system activation in the brain [Pourahmad, 2020].

Another potential mechanism of action for IVIG in treating post-COVID neuropsychiatric symptoms is its ability to modulate the function of immune cells, such as T cells and monocytes [Ballou, 2014]. These cells play a critical role in the immune response to the virus and may contribute to the development of neurological symptoms. By modulating their function, IVIG may help reduce the severity of these symptoms.

It's important to note that the mechanisms described above are based on observations from preclinical and clinical studies, and more research is needed to fully understand the exact ways in which IVIG may affect post-COVID neuropsychiatric symptoms. Additionally, it's important to recognize that IVIG is a complex mixture of antibodies and other components, and different components may have different effects on the immune system and the brain.

**4.4 Safety of IVIG**

Intravenous immunoglobulin (IVIG) is a generally safe treatment for appropriate indications, but potential side effects and adverse events can occur. Common side effects include infusion reactions, headache, fatigue, muscle aches, and nausea [Katz, 2007]. Rare but serious adverse events include thrombosis, aseptic meningitis, and renal impairment. It's important to monitor patients closely

for potential side effects and adverse events and adjust the treatment plan as needed based on the patient's medical history. Some possible long-term effects of IVIG may include kidney damage, blood clots, and allergic reactions [Muccioli, 2021]. However, these side effects are relatively rare, and the benefits of IVIG usually outweigh the risks. The specific long-term effects of IVIG may depend on the individual patient and the condition being treated.

A study conducted on individuals with multiple sclerosis found that the primary negative effect reported during the initial dosage period was headache, which was experienced by 12.6% of patients. During the maintenance period, the annual incidence of adverse events was 4.4% in the first year and showed a decreasing trend as treatment progressed. There were no reports of severe negative effects, leading to the conclusion that IVIG is a safe therapy for multiple sclerosis patients in both the short and long term [Katz, 2007].

#### **4.5 Efficacy of Intravenous Immunoglobulins**

The results of these studies have been varied and sometimes inconsistent, with some indicating a positive impact of IVIG treatment while others are less clear.

One of the studies conducted by Efe found that IVIG treatment had a significant positive impact on these patients' symptoms [Efe, 2022]. These symptoms included somatic complaints, restrictive food intake, OCD symptoms, severe anxiety with hallucinations, depression, and even mild neurological symptoms. The patients also showed weight gain, which was a good sign of their overall improvement.

However, the study by Zahed failed to provide sufficient information on the specifics of the IVIG treatment, including dosage, timing, and relationship to other treatments, making it difficult to assess the efficacy of the treatment accurately [Zahed, 2022]. The contribution of IVIG treatment to the improvement of the patient in the study by O'Leary was also unclear [O'Leary, 2021]. On the other hand, Della Corte's study showed that IVIG treatment resulted in a progressive reduction of involuntary movements and improved cognitive functions [Della Corte, 2022].

In Muccioli's study, all patients experienced complete electroclinical recovery following IVIG treatment, with an initial improvement in neuropsychiatric symptoms observed after 3.4 days on average [Muccioli, 2021]. It is important to note that other immunotherapies, such as tocilizumab and steroids, were also mentioned in the paper by Muccioli [Muccioli, 2021]. However, the relationship between these treatments and IVIG treatment, as well as the timing specifics, is unknown.

There have been a few case reports and small studies suggesting that IVIG may be effective in treating certain neuropsychiatric symptoms associated with COVID-19, such as confusion, disorientation, and memory loss. However, these studies have been limited in size and scope, and more robust research is needed to confirm these findings and determine the optimal dosing and duration of treatment. The wide range of neuropsychiatric symptoms may not all respond to IVIG treatment.

#### **4.6 Implications for clinical practice**

In conclusion, the results of the studies regarding the effectiveness of IVIG treatment for post-COVID-19 neuropsychiatric symptoms have been varied and sometimes inconclusive. Some studies have indicated IVIG treatment's positive impact on various medical conditions. For instance, Efe [Efe, 2022]'s study showed that the treatment significantly decreased symptoms such as somatic complaints, restrictive food intake, OCD symptoms, severe anxiety with hallucinations, depression, and even mild neurological symptoms, and weight gain in the patients. Della Corte [Della Corte, 2022]'s study showed that IVIG treatment significantly reduced involuntary movements and improved cognitive functions. Muccioli's study showed complete electroclinical recovery following IVIG treatment [Muccioli, 2021].

While these studies provide some promising results, it is important to note that further research is needed to fully understand the impact of IVIG treatment on patients with different medical conditions. This is because some of the studies, such as Zahed's, failed to provide sufficient information on the specifics of the IVIG treatment, making it difficult to assess its efficacy accurately [Zahed, 2022]. The relationship between IVIG treatment and other immunotherapies, such as tocilizumab and steroids, is unclear and may cause confusion.

The use of intravenous immunoglobulin (IVIG) for the treatment of post-COVID neuropsychiatric symptoms is still being studied and its efficacy is not well established. Therefore, it's difficult to determine which patients would benefit most from this treatment.

IVIG has been used as a treatment for other neurological conditions that are associated with immune system dysregulation and inflammation, such as Guillain-Barré syndrome and multiple sclerosis [Katz, 2007]. In these conditions, patients who have severe or rapidly progressive symptoms may be more likely to benefit from IVIG treatment.

## 5. Conclusion

The use of IVIG to treat neuropsychiatric symptoms after COVID-19 infection is still a relatively new field of study, and the results of the studies involving this treatment have been mixed. Some studies have shown promising results, with patients reporting improvement in symptoms such as fatigue, cognitive impairment, and mood disorders. However, other studies have not shown significant improvement in these symptoms with IVIG treatment.

Despite the mixed results, the positive outcomes observed in some studies suggest that IVIG may have potential as a treatment option for neuropsychiatric symptoms after COVID-19 infection. Further research is necessary, however, to fully understand its effectiveness and to determine the best way to apply it in clinical practice. This may include determining the optimal dosing and duration of treatment, identifying the patient population most likely to benefit from IVIG treatment, and understanding the mechanisms by which IVIG may be effective in treating these symptoms.

In addition to its potential benefits, the safety of IVIG for treating neuropsychiatric symptoms after COVID-19 infection must also be thoroughly evaluated. This includes determining the long-term safety of IVIG for this purpose and identifying any potential side effects or adverse events associated with its use.

In conclusion, the results of the studies involving the treatment of post-COVID neuropsychiatric symptoms with IVIG have been mixed, but the positive outcomes observed suggest that it may be a promising treatment option. Further research is necessary, however, to fully understand its effectiveness and proper application.

## Declarations

There were no sources of financial or non-financial support for this review.

The authors declare no competing interests.

**Ethical approval:** Due to the nature of research, ethical approval was not required.

**Informed consent:** Due to the nature of the research, informed consent was not required.

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