



# Post COVID-19 neuropsychiatric complications and therapeutic role for TNF- $\alpha$ inhibitors: a case series study

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## Abstract

**Background** The post-COVID syndrome is the various physical and neuropsychiatric symptoms after the acute phase of COVID-19. The understanding of pathophysiology of this syndrome and its treatment need to further studies. This study aimed to present three cases of neuropsychiatric symptoms after COVID-19 and effective treatments in these patients.

**Case presentation** Three patients with new or progressively neuropsychiatric symptoms such as seizures, attention difficulties, insomnia, confusion and etc., were referred to our clinic about 8 months after severe COVID-19 infection. The patients were assessed with extensive workup includes a neurological exam, brain MRI, LORETA scan, and biochemical and levels of inflammatory serum markers. All patients had elevated levels of TNF- $\alpha$ , poor neurological exam, and abnormal reports of MRI or LORETA scan. Diagnosis of post- COVID neuropsychiatric complications was made for the patients. TNF inhibition with Adalimumab (40 mg/weekly for a month) was initiated for the patients and led to a dramatic improvement of all symptoms.

**Conclusions** To our knowledge, this report is the first case series study that suggests TNF inhibitors in the treatment of post-COVID-19 syndrome, especially neuropsychological complications. However, future studies should evaluate the best therapeutic options for this syndrome.

**Keywords** COVID-19 · Post- infectious · Neurology · Complications · Treatment · TNF- $\alpha$  inhibitors · Long term

## Introduction

More than 1.5 years after the appearance of the COVID-19 pandemic, morbidity, mortality, and the destructive economic and social effects of this disease continue in the world. Although COVID-19 affects the respiratory and gastrointestinal systems, neuropsychological manifestations in patients have been found in the early stage of disease [1, 2]. Some studies have been shown that some neuropsychiatric symptoms are before, during, or after respiratory insufficiency and it suggests independent neurological involvement in this disease [3, 4].

In early 2020, it has been shown that several patients after the acute phase of the disease had physical and neuropsychiatric symptoms persisting for several weeks, months, or years, named post-COVID syndrome. However, the post-COVID-19 syndrome has been reported among hospitalized patients with severe disease, recently, new clinical manifestations, such as rare neurological and thromboembolic complications without a previous history have been recognized

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[4, 5]. A direct infection of the neurological system and severe reaction to a viral disease outside the nervous system can be reason of neurological feature.

The pathophysiology of post-COVID-19 syndrome is unknown and there is little evidence suggesting brain involvement persists [3]. Prolonged inflammation is a main factor in the pathogenesis of post-COVID-19 syndrome. Inflammatory cytokines could pass the blood-brain barrier (BBB) and could remind in brain tissue and lead to CNS, brain stem, and other parts of brain complications [6].

While the burden of neuropsychiatric complications is high, the soon treatment of these disorders is important. As a result, COVID-19 survivors with persistent impaired brain function in the post-COVID-19 phase may benefit from early and close follow-up with a neurologist and psychiatrist in survivor clinics. In many patients, standard therapies are not effective and require new treatments [7].

In this study, we reported the cases of post-COVID with neuropsychiatric complications and effective treatments in these people.

## Case description

### • Case 1

A 32-year-old woman was referred to our clinic with poly-symptomatic neuropsychiatric presentation, autonomic dysfunction, polymorphic movement disorder, attention difficulties, hearing loss, and episodes of fall followed by clonic seizure, June 2021.

She had a history of two febrile seizures as a child. Seven months earlier, she was admitted to the hospital based on her respiratory symptoms and with diagnosing severe COVID-19 infection. Two months after she was discharged, she noticed dis-coordination, attention, and connection difficulties and she was admitted to the hospital for a week. The comprehensive neurologic, laboratory tests, neurological evoked assessments, and brain imaging includes PET scanning were done with another specialist's teams, and the only valued findings were positive serological COVID-19 IgG, Anti-GAD, and Anti-TPO. At admission, she was received two periods of corticosteroid pulse-therapy, also plasmapheresis. Despite prescribing anticonvulsants, antidepressants and low-dose prednisolone, she had progressively worsened symptoms when she was referred to our clinic. In the neuropsychiatric examination, we found overt gait ataxia, gaze ataxia, both vertical and gazed-evoked nystagmus, impaired attention and concentration, impaired tandem gait, and partial secondary generalized tonic seizure attacks. Awake-EEG, LORETA scan, and hypothesized inflammatory serum markers were performed. EEG and brain MRI were normal and no abnormalities were

detected. In the LORETA scan, the level of Beta band activity in right temporoparietal areas was decreased and alpha activity was decremented in left motor cortex, left prefrontal, and left orbitofrontal cortices. Among inflammatory serum markers, TNF- $\alpha$  was increased. Other lab tests revealed normal CBC and biochemical tests.

Considering all the evidence, post-COVID encephalitis diagnose was considered for the patient and she underwent Adalimumab 40 mg /weekly for a month. After one month of clinical follow-up, seizure attacks, coordination were improved.

### • Case 2

A 46-year-old woman was presented with new symptoms such as early morning awakening, lower extremities restlessness and stretching, and constant throbbing occipital headaches after recovery of COVID-19 infection, 4 months ago. Also, palpitation, shortening of breath, low back pain, and gustatory and smelling loss since COVID 19 infection. In the neurological exam, there was dis-coordination with impaired tandem gait and mild gazed-induced horizontal nystagmus.

She was evaluated by Brain MRI, LORETA scan, and lab tests. Brain MRI had no abnormalities. There was slow-wave activity in both para-hippocampal cortices and Beta activity revealed decreasing in the right superior parietal cortex within LORETA scan. Lab tests were shown increased TNF- $\alpha$  and other tests were normal.

In the past history, she was diagnosed with Behcet's disease and she was taken Colchicine 1 mg daily. History of autoimmune disease and clinical presentation and disease course lead to diagnosis of delayed post-infection immune-mediated encephalitis was made for this patient. Therefore, we prescribed Adalimumab 40 mg /weekly for a month. Thirty days later, all symptoms were improved.

### • Case 3

A 45-year-old woman with a history of COVID-19 in January 2021, spondyloarthritis and chronic migraine headaches from 11 months before COVID infection, was referred with new-onset symptoms in our clinic. Also, she had a history of seizures since she was 6 years old. She took Sulfasalazine, Prednisolone, and Carbamazepine for her diseases.

In October 2021, she was referred with new complaints of insomnia, confusion, and also she had progressively worsened generalized somatic pain in both joints and muscles with constant and steady, pulsating and throbbing, stabbing or pinching nature. New symptoms were progressively developed 10 months after COVID infection. In the neuropsychiatric exam, she had mild cog-

nitive impairment, worsened migraine attacks, mild dis-coordination in tandem gait, tender arthralgia and, myalgia in four extremities. In her lab tests, she had elevated levels of TNF- $\alpha$ , beta-Amyloid 1–42, IL-6, and IL-1. Brain MRI was normal in general except for some subcortical non-enhanced white matter lesions. Diagnosis of post- COVID encephalitis was made for this patient. Therefore, we prescribed Adalimumab 40 mg / weekly for a month. After two weeks, all symptoms were improved.

## Discussion

In this case series, we described the cases of the post-COVID-19 syndrome, which led to neuropsychiatric complications, about 8 months after the COVID infection. To our knowledge, this is the first case series that presented the role of anti-TNF therapy in post-COVID-19 syndrome.

In the acute phase of severe COVID-19 infection, evidence has shown that SARS-CoV-2 can enter into the brain through angiotensin-converting enzyme 2 (ACE 2) receptors in the olfactory epithelium, neurons, and glial cells, finally resulting in different regions of the brain and CNS damage, and inflammation. Furthermore, pro-inflammatory cytokines can directly cross the BBB and lead to brain damage [6, 8]. Additionally, the presence of neuroinflammatory responses after severe COVID-19 has been reported in many populations and it suggests that the maintenance of prolonged inflammation is a key role in the pathogenesis of most post-COVID manifestations [4]. Also, endothelial damage, thrombosis, and nervous system dysfunction are the other pathogenetic mechanisms in post-COVID syndrome [4, 9].

However, many pro-inflammatory cytokines and mediators such as IL-6, IL-1, interferon  $\gamma$ , and IL-1 are effective in neuropsychological post-COVID complications, it seems that TNF- $\alpha$  is the most important factor in this disease. TNF- $\alpha$  is a potent pro-inflammatory cytokine with a major role in initiating a cascade of activation of other cytokines and growth factors in inflammatory diseases [10, 11].

Some evidence has reported that when TNF- $\alpha$  is blocked, the concentrations of IL-6 and IL-1 are reduced in less than 12 hours [11, 12]. Based on this theory, anti- TNF antibodies have been used in severe autoimmune inflammatory diseases such as rheumatoid arthritis [13]. Also, preclinical studies showed that inhibition of TNF reduces the severe respiratory diseases [14].

While the use of immunomodulatory drugs such as IL-6 antagonists during the current pandemic raised many concerns, some studies described a protective role for TNF inhibitors among patients with autoimmune diseases who developed COVID-19 [15, 16]. However, the results of a few clinical trials about the use of TNF inhibitors as an effective

drug for COVID-19 patients without a history of autoimmune diseases have not been published [17, 18].

On the other hand, due to the importance of pro-inflammatory factors in the pathogenesis of post-COVID syndromes, this suggests a possible role of TNF inhibitors in the treatment of post COVID infection. The results of our cases showed that in all patients, whether patients with a history of autoimmune patients or those who did not, their TNF levels were high. Therefore, we agreed with this hypothesis that anti -TNF therapy might be appropriate for neuropsychiatric post-COVID patients. The results of follow-up showed that symptoms of patients were improved and this therapy might be effective.

In this study, some limitations should be recognized. The case series can be prone to bias, limiting its generalizability to larger populations of patients. However, a case series can provide information that allows hypotheses to develop, leading to further advanced studies.

## Conclusion

This study suggests TNF inhibitors in the treatment of post-COVID-19 syndrome, especially neuropsychological complications. However, future studies should evaluate the best therapeutic options for this syndrome.

**Abbreviations** *COVID-19*: Coronavirus disease 2019; *TNF- $\alpha$* : Tumor necrosis factor alpha; *MRI*: Magnetic resonance imaging; *LORETA*: Low-resolution electromagnetic tomography analysis; *CNS*: Central nervous system; *EEG*: Electroencephalography; *PET scan*: Positron emission tomography scan; *IgG*: Immunoglobulin G; *Anti-GAD*: Anti-glutamic acid decarboxylase; *Anti-TPO*: Anti-thyroid peroxidase; *DTR*: Deep Tendon Reflexes; *MOCA*: Montreal Cognitive Assessment; *IL*: Interleukin; *BD*: Twice a day; *ACE 2*: Angiotensin-converting enzyme 2; *SARS-CoV-2*: Severe acute respiratory syndrome coronavirus 2

## Declarations

**Consent for publication** All patients provided consent to published identified information for this case series report.

**Competing interests** The authors declare that they have no competing interests.

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