NL Neurology Letters

Review Article

https://doi.org/10.52547/nl.1.2.69

Central nervous system autoimmune diseases associated with COVID-19: Comprehensive review

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Abstract

The first appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) named coronavirus disease 2019 (COVID-19) was reported from Wuhan in December 2019. While this virus displays several respiratory manifestations such as severe pneumonia and acute respiratory distress syndrome, there are several reports of nervous system involvement in the affected patients. Currently, there is a growing number of cases with central nervous system (CNS) autoimmune diseases (ADs) including autoimmune encephalitis (AE), neuromyelitis optica spectrum disorder (NMOSD), CNS vasculitis, acute disseminated encephalomyelitis (ADEM), and multiple sclerosis (MS) secondary to COVID-19 infection. Symptoms of these diseases vary from mainly drowsiness, delirium, and motor deficits in ADEM, MS, and AE and also visual impairment, and sensory problems in NMOSD and transverse myelitis patients. The severity of COVID-19 symptoms was also different from disease to disease. Based on the previous studies moderate corticosteroid therapy or other medication such as intravenous human immunoglobulins (IVIG), plasma exchange (PLEX) is suggested for the treatment of CNS ADs in the COVID patients. Also, patients with a previous history of ADs and other comorbidities such as hypertension, diabetes mellitus, hypercholesterolemia, and ischemic heart disease are at greater risk to develop severe complications of COVID compared to other patients. Current pieces of evidence demonstrated that CNS ADs can occur due to COVID-19 infection and the health care system should attention to CNS ADs as a complication of COVID-19. However, further investigations are strongly needed to confirm these findings.

Keywords: Central Nervous System; COVID-19; Autoimmune Disease

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Published online 30 December 2022

Cite this article as: Nabizadeh, F., Pirahesh, K., Sodeifian, F., Hashemi, S. M., Balabandian, M., Rezaeimanesh, N., Naser Moghadasi, A. Central nervous system autoimmune diseases associated with COVID-19: Comprehensive review. Neurology Letters, 2022; 1(2): 69-77. doi: 10.52547/nl.1.2.69.

Introduction

The first appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) named coronavirus disease 2019 (COVID-19) was reported from Wuhan in December 2019 which lead to one of the greatest pandemics in the history of the world (1). While this virus displays several respiratory manifestations such as severe pneumonia and acute respiratory distress syndrome (ARDS), there are several reports of nervous system involvement in the affected patients (2). These neurological manifestations included a range from neurodegenerative disorders to autoimmune diseases including Guillain–Barre syndrome, encephalitis, stroke, seizure, and headache (2).

Currently, shreds of evidence indicate that COVID-19 may cause neurological disorders via direct viral attack or indirectly trigger immune-inflammatory mechanisms which leads to immune-mediated neurological disorders (3, 4). Furthermore, there is a growing number of cases with central nervous system (CNS) autoimmune diseases (ADs) including autoimmune encephalitis, neuromyelitis optica, CNS vasculitis, optica neuritis, acute disseminated encephalomyelitis (ADEM),

myelitis, and multiple sclerosis (MS) secondary to COVID-19 infection which can illustrate the potential role of this virus in the pathophysiology of such disorders (5-8). In addition to inflammatory processes, it seems that neurodegeneration is also involved in the onset of these disorders secondary to COVID-19 (9-11). However, there is no clear and comprehensive evidence on the prevalence, risk factors, clinical symptoms, and management of patients who develop CNS ADs due to COVID-19 infection.

In this review, we will summarize the available evidence regarding the CNS ADs associated with COVID-19 infection to guide management protocols and clinical practice. Also, we will specifically discuss the pathological mechanisms between CNS ADs and COVID-19, and we will highlight the demographical features and comorbidities which make a person susceptible to developing CNS ADs.

Does any relationship exist between autoimmune disease and developing COVID-19 infection?

The SARS-CoV-2 infection causes a dysregulated immune response and enhanced expression of inflammatory cytokines, resulting in the production of autoantibodies and loss of immune tolerance, which could lead to the development of autoimmune diseases (ADs) (9). Several studies have reported the development of ADs as a complication of SARS-CoV-2 infection. Acute transverse myelitis, autoimmune encephalitis, acute necrotizing myelitis, and CNS vasculitis are among ADs COVID-19 complications (10-13). Bonometti et al. reported the first case of systemic lupus erythematosus (SLE) following COVID-19 infection (14). Moreover, these patients should be re-evaluated at viral infection resolution to assure that there is not trigger towards ADs development (14). Another reported the first case of Guillain-Barre syndrome (GBS) triggered by SARS-CoV-2 infection (15). According to this report, GBS could develop after paucisymptomatic infection or even in an asymptomatic patient. Furthermore, genetic predisposition of DRB1*03:01, HLA-A33, and DBQ1*05:01 in this patient could also contribute to the development of SARS-CoV-2-induced Guillain-Barre syndrome (Si-GBS). And at last, the ELISA assay revealed a significant increase in IL-8 levels in CSF, proposing the possible IL-8 pathway in the pathogenesis of Si-GBS. Therefore, in COVID-19 infected patients suspected of autoimmune diseases; genetic testing could be considered to distinguish these patients from the differential diagnosis. Moreover, autoimmune diseases could develop in asymptomatic COVID-19 infection, which could be confirmed by detecting inflammatory cytokines and autoantibodies in cerebrospinal fluid (CSF) of patients (15). However, in the major number of COVID-19 patients with neurological manifestations, SARS-CoV-2 RNA could not be detected in CSF.

As we know viral infections plays an important role in development of some CNS autoimmune disease such as NMOSD and MS (16). As well, during the SARS-CoV-2 pandemic there were reports of CNS ADs disease secondary to COVID-19 infection which may suggested the possible role of this virus in pathophysiology of these diseases (13, 17-19).

One of the suggested links between CNS ADs and COVID-19 is the direct attack of virus to the CNS via entering host cells and causing neurological manifestation due to binding with Angiotensin-converting enzyme 2 (ACE2) (20). However, while most of the patients who developed CNS ADs were negative for SARS-CoV-2 PCR in CSF, the virus may lead to CNS ADs via other possible mechanisms.

SARS-CoV-2 can leads to demyelinating via decrease number of immune cells such as CD4+ T cells, CD8+ T cells, B cells, and NK cells or provoke autoimmune reactions (21). In autoimmune reaction scenario the antibodies which produced against SARS-CoV-2, attacks neurons and vessels endothelial cells resulted in autoimmune encephalitis or cerebral edema (22). Another mechanism is the cytokine storm causes by toll-like receptors (TLRs) activated by SARS-CoV-2 (23). These cytokines cause neuronal and oligodendrocyte death and finally demyelination (24).

CNS autoimmune diseases prevalence in COVID-19

Besides neurological manifestations of COVID-19, growing attention to neuroimmune manifestations has emerged. CNS Neuroimmune disorders in COVID-19 patients compromise a spectrum of complications including encephalitis, myelitis, optic neuritis, and acute disseminated encephalomyelitis (ADEM), and other atypical diseases.

Infections, as well as SARS-COV-2, can trigger autoimmune reactions and make several diseases more prevalent than before (25). According to a systematic review, autoimmune encephalitis had the highest prevalence among CNS autoimmune diseases in hospitalized COVID-19 patients accounting for 0.1-0.2% followed by myelitis and optic neuritis with a prevalence of 0.1% (26).

Autoimmune encephalitis

Encephalopathy in COVID-19 patients is a condition that results from multiple factors including hypoxia, toxic metabolites, medications, multi-organ failure in sepsis, seizures, and immune dysregulation (27). Various types of autoimmune encephalitis have been reported in COVID-19 patients including Limbic encephalitis, Anti-NMDA receptor encephalitis (28), autoimmune encephalitis presenting as new-onset refractory status epilepticus (NORSE) (29), and Steroid-responsive encephalitis. The development of encephalitis mostly occurred after COVID-19 initial symptoms (28). To distinguish encephalitis with autoimmune origin from primary infection of the CNS, here we present pieces of evidence from reported cases that support the encephalitis autoimmune origin hypothesis. First, the occurrence of encephalitis was mostly after the infection symptoms disappearance and the reverse-transcription polymerase chain reaction (RT-PCR) was turn to negative (30). Second, high titer of IgG antineuronal autoantibodies in some cases (30), however, this observation seems to be controversial, since there were also reports of “antibody-negative” autoimmune encephalitis. Third, clinical resolution of symptoms after immunomodulatory treatments like steroid therapies (11).

According to diagnostic criteria of autoimmune encephalitis, MRI markers are used for encephalitis diagnosis (31) and in SARS-COV-2 infected patients with normal MRI, fluorodeoxyglucose (18F) positron emission tomography (F-FDG PET) revealed diffuse cortical hypometabolism pattern. This observation suggests a potential role of PET as an early diagnostic tool (30).

Reports from Anti-NMDA receptor encephalitis were more concerned with prominent psychotic disorders and seizures (28). Interestingly also in these cases, MRI did not show any remarkable changes in patients with positive anti-NMDA receptors antibodies on CSF (32).

Neuromyelitis Optica

Neuromyelitis Optica spectrum disorder (NMOSD) is another autoimmune disturbance that can be secondary to COVID-19, which involves autoantibodies most commonly against water channel aquaporin-4 (Anti AQP-4 IgG1)(33). Viral infections as well as COVID-19, allow passage of the antibodies with increasing blood-brain barrier (BBB) permeability. This autoimmune reaction results in damage to optic nerves and the spinal cord (34). Also, the pieces of evidence showed that the total number of cases with NMOSD due to COVID-19 is higher compared to other CNS ADs (17-19).

Myelitis

Myelitis, especially transverse myelitis (TM) is caused by infections, autoimmune diseases of CNS, systemic autoimmune disorders, and also it can occur with an unknown origin which results in inflammation of the spinal cord and damage to the myelin (35). SARS-CoV-2 may possibly increase risk of TM, via autoimmune reactions (36). While one of the suggested mechanism for ADs due to viral infections is the direct attack of virus, but the reported myelitis cases did not detect virus in CSF which indicated that the autoimmune response may be involved in the pathophysiology of the disease (10, 37-40). There is a hypothesis revealed that several factors including IL-2, 6, 7, and 10, and tumor necrotizing α factor (TNF- α) causing damage to myelin, and considered as initiators of inflammation in this setting (40). Most of the cases of myelitis reported after the active phase of COVID-19 infection and ventral horn affection pattern was reported in these patients, which favors viral myelitis (40, 41). As our knowledge, there are more than 10 cases reported with myelitis along with COVID-19 infections (37-40)

CNS vasculitis

Less frequently, there were some reports of CNS vasculitis proven by radiological evidence, which were alleviated by steroid therapy and IL-1 and IL-6 pathway blockage (42). MRI patterns suggesting inflammation and ischemia in CNS can be detected in these patients (13). There are few cases of CNS vasculitis in COVID-19 patients which are considered as a unique neurological manifestation of the coronavirus (43).

3.5. Multiple sclerosis (MS)

While other CNS ADs including NMOSD, ADEM, and myelitis reported following COVID-19, MS exacerbation after COVID-19 infection was limited to few studies (44-46). The MS exacerbation may be caused by inflammation initiated by Toll-like receptors (TLRs) which recognize invading virus, cytokine storm in severe cases with disruption of BBB, direct invasion of the virus, and a potential demyelinating reaction caused by COVID-19 (46).

Optic Neuritis

Optic neuritis is the most common demyelinating disorder of the optic nerve which is usually associated with MS and occurs with sudden visual loss and pain in the affected eye (47). While the ocular manifestation secondary to COVID-19 is a rare condition, there are few cases of optic neuritis due to COVID-19 infection (5, 48, 49). Bilateral optic neuritis is a rare phenomenon that is observed in a patient with confirmed COVID-19 infection (49). It seems that COVID-19 infection may trigger the production of MOG antibodies and autoimmune response which resulted in optic neuritis (50).

Acute disseminated encephalomyelitis (ADEM)

ADEM is another reported immune-mediated neurological manifestation of COVID-19 infection which is recognized by encephalopathy, neurological symptoms, and abnormal demyelinating in brain MRI (7). ADEM is mostly observed due to viral infection and rarely vaccination while, since the SARS-COV-2 outbreak, there was an emerging body of cases reported with ADEM after COVID-19 infection which is assumed to be due to immune response (51). In these patients, the MRI abnormalities may be caused by the direct viral attack, demyelinating process, or toxic metabolic components (6, 52-54).

CNS Autoimmune disease symptoms in COVID-19 patients

Most COVID-19 infected patients remained without any signs and symptoms, but the most serious effect of COVID-19 is observed in the respiratory system resulting in severe acute respiratory syndrome (SARS) (55). However, various neurologic manifestations have been reported during the pandemic associated with COVID-19. This has been remarkable enough to include COVID-19 in differential diagnosis for the patients presented with neurologic symptoms during the COVID-19 outbreak (56). Different theories were suggested for explaining this association. Direct viral invasion may be possible due to the presence of Angiotensin-converting enzyme 2 (ACE2) receptors (main receptor for beta coronavirus entry) in CNS, particularly in the brain stem; however, most studies observed no presence of viral nucleic acid in CSF RT-PCR (57). Furthermore, it was demonstrated that virus attacks supporting cells in the olfactory epithelium, rather than the neurons which indicates that the direct viral invasion is not feasible for explaining these symptoms (58). Another theory in this regard is the immune-mediated damage either due to autoimmunity or hyper-inflammation syndrome (57). This seems more plausible because of the prevailing presence of anti-CNS-specific antigens and high titers of cytokines in these patients (58).

Here we provide neurologic symptoms of multiple types of CNS autoimmune diseases. It is noteworthy to mention that different investigators have used various terms to describe these neurologic conditions which can make it harder to compare present data. Therefore, we have relied on general descriptions more.

Autoimmune encephalitis

Studies have mainly focused on 3 types of encephalitis which were suspected to have autoimmune causes in patients with COVID-19: Limbic encephalitis (LE), Anti-NMDA receptor encephalitis, and autoimmune encephalitis presenting as new-onset refractory status epilepticus (NORSE).

The most common symptoms in these patients included mental confusion, drowsiness, delirium, deficits in motor functions, and seizures. However, all of these symptoms weren't constantly present in all of the cases and a various clinical presentation was rather observed (4, 11, 28-30, 32, 59-67).

Disease symptoms for LE were mostly similar to other encephalitis types at the beginning. However, the onset of these symptoms was delayed. Also, abnormalities were detected in CSF analyses of these patients (such as hyperproteinorrachia, pleocytosis, etc.). Also, RT-PCR results were negative for COVID-19 viral nucleic acid in CSF according to studies in LE. In reported cases, metabolic functions were evaluated as normal, and acute onset delirium, altered mental status, cognitive impairment, status epilepticus, focal motor deficits, confusion, diaphoresis, dysphasia, and impaired orientation were observed as well (4, 60, 61, 63, 64, 66).

Most Anti-NMDA receptor encephalitis cases were reported with insomnia, increased psychomotor activity (such as orofacial dyskinesias), cognitive impairment, and seizures, indicating a simultaneous presentation of neurologic and psychiatric symptoms. Autoantibody testing demonstrated NMDAR-IgG positivity in the CSF, however, the results for the serum test weren't consistent. Early MRI Images didn't show any significant changes in the brain in any of the recently reported cases (28, 32, 62, 65, 67).

COVID-19 patients with autoimmune encephalitis presenting as NORSE commonly developed status epilepticus as the first neurologic symptoms. CSF analysis for abnormalities was negative except for one case of positive onconeural antibody and anti-neuronal surface antigens antibody. Also, MRIs were negative at the early stages of reported cases while Electroencephalography (EEG) results showed impaired delta waves. Furthermore, there were no signs of cerebral thrombosis in any of these cases (29, 59).

Some other cases of encephalitis were also reported with no evidence of autoimmune bases, such as steroid-responsive encephalitis, indicating a rather CNS inflammatory-mediated involvement (60).

CNS vasculitis

Few cases of COVID-19 patients with neurologic manifestations were reported to develop CNS vasculitis to date. Along with other respiratory and immunologic symptoms associated with COVID-19, drowsiness and impairment of arousal were seen in these patients. CT images revealed blood related hyperdensities in various cortical and subcortical brain regions while multiple hypodensities were reported in one of the cases (43). MRI complied with these results which showed extensive ischemic lesions with restricted diffusion in multiple brain areas. Moreover, electroencephalogram revealed theta and delta pattern. Tetraplegia with bilateral mute plantar response was reported in one of the cases as well (13, 43). In one of the cases, Angiography was performed and no abnormality in intra and extra cranial vessels were found (43).

Multiple Sclerosis

Very few observations of MS being developed or exacerbated due to a COVID-19 infection have been reported. In one case, decreased visual acuity was reported following COVID infection. Moreover, MRI indicated demyelinating lesions of CNS along with right optic nerve inflammation suggesting a connection between MS and COVID-19 (45). Despite the well-established connection between Toll-Like receptors and MS, in addition to the role of these receptors in recognizing pathogens, there is not enough evidence to support this association (46). In another reported case with onset of MS concurrent with COVID-19, the blurred vision described as a first sign of MS and then loss the smell and taste sense. In addition, eye movement was painful and visual acuity was decreased (44). Furthermore, chest CT scan was normal, and brain MRI showed periventricular and pericallosal lesions which were not enhanced with gadolinium and also optic nerve involvement was reported (44).

Myelitis

Acute transverse, acute flaccid, and acute necrotizing myelitis with acute motor axonal neuropathy have been reported as neurologic complications of COVID-19 involving the spinal cord. Tingling and numbness in fingers and toes were usually present at the onset of the disease. Later on, paresthesia progressed to quadriplegia in the upper and lower extremities in addition to the loss of sensation (10, 36, 38, 39, 41, 68-73), while some cases were reported with paraparesis (10, 39, 40, 74). In the most reported patients with myelitis, affected sphincter functions resulted in urinary retention, constipation, bowel or urinary incontinence. It is noteworthy to mention that impaired sphincter functions (especially urinary retention) were the most common reason for hospital admission in these patients (36, 68, 70, 73). Furthermore, cerebral functions were evaluated as normal. In nearly all of these patients, T2 patchy hyperintensities were observed in the mostly lower cervical and upper thoracic regions. The lymphocyte pleocytosis was the only abnormality detected in the CSF analysis of these patients. In addition, CSF PCR analysis for any viral nucleic acid or bacteria was negative (10, 36, 38, 39, 41, 68-73). Interestingly, in a case reported by Zachariadis et al, no abnormalities were found in the brain and

spinal cord MRI, however, severe neurologic symptoms were still present (37).

Neuromyelitis Optica

Considering the rarity of NMOSD, very few reports have been published concerning the symptoms of COVID-19 patients who developed these disorders. The onset of the disease usually involved visual impairment and the rest of the symptoms were similar to those of acute myelitis including numbness of fingers, weakness of lower limbs, and sensory deficits indicating thoracic levels. In one case, urinary incontinence was observed as well. The MRI revealed no intracranial abnormalities in these patients while spinal abnormalities were consistently reported. In most of these cases, CSF analyses for aquaporin-4 immunoglobulin G (AQP4-IgG) were positive (18, 75), except one case with the positive result of the anti-MOG-IgG test (34). Common COVID-19 disease symptoms such as cough, fever, headache, fatigue, and myalgia were present in most of the patients who already had NMOSD before COVID-19 infection while gastrointestinal complications were also frequent (76).

Optic neuritis

All of the reported cases of optic neuritis were administered to care due to visual problems with the onset of symptoms such as ocular pain and blurred vision. In the two cases, visual symptoms appeared in one eye initially and then progressed to the other one, resulting in bilateral visual impairment (49, 77). Optic disc edema was also commonly seen among these patients. In a progressed optic neuritis case, the temporary complete visual loss was reported as well (49). Also, there are no symptoms of CNS inflammation such as limb weakness in these patients. Cranial and spine MRI were unremarkable, whereas optic nerves were affected. Multiple markers such as enhancement, thickening, hyperintensity, and edema of optic nerve suggested optic neuritis in these patients (5, 48, 49, 77).

4.7. Acute Disseminating Encephalomyelitis (ADEM)

As a rare presentation of autoimmune inflammation of CNS, ADEM has been reported in numerous cases of COVID-19 with loss of consciousness, ataxia, and motor weakness (6, 7, 51, 52, 54, 78, 79). In most of these cases, deep tendon reflexes were depressed or asymmetric (6, 52, 54, 79). Moreover, visual disturbances were reported in some of the cases (7, 51). According to reported cases, there are no signs of sphincter abnormalities in any of the COVID-19 patients developing ADEM. Brain MRI showed hyperintense lesions involving various locations such as cortical, subcortical, juxtacortical, deep white, and gray matter in these patients (6, 51, 54, 78, 79). Furthermore, CSF analyses were normal except for oligoclonal bands which were reported positive in some of the cases (7, 51, 78). In cases with evaluated EEG, diffuse slowing without epileptiform abnormalities was also reported (51, 52).

The severity of COVID-19 infection in patients with CNS autoimmune diseases

The severity of COVID-19 infection in patients manifesting neurologic symptoms varies greatly. Due to the different nature of these symptoms, different outcomes were seen. Some of the patients experienced only mild respiratory symptoms while tested positive for COVID-19 and had serious neurologic manifestations (60), also cases with respiratory failure along with neurologic symptoms were reported as well (59).

Most of the patients diagnosed with autoimmune encephalitis were presented with mild to moderate respiratory symptoms at onset, while the main reason for hospital admission was neurologic symptoms (especially seizures) (4, 11, 30, 62, 63, 66). However, in some patients with comorbidities such as arterial hypertension or higher age, severe respiratory failure symptoms were observed (4, 59, 64). In a study of 29 COVID-19 patients with neurologic manifestations, it was demonstrated that 27% required critical care admission, although, most of them which were diagnosed with ischemic stroke and fewer had an inflammatory basis for their symptoms (61). Interestingly, in numerous cases, neurologic manifestations were seen without any severe respiratory symptoms, especially in pediatric patients and the biggest threat for these patients was mostly neurological complications (62, 67).

Observed cases of CNS vasculitis and COVID-19 were usually aged higher than 60 suggesting the possibility of a more severe disease course due to higher age. The inflammatory syndrome was seen in these patients, including fever, cough, and fatigue. Chest CT also confirmed the presence of pneumonia (13, 43). Also, a one CNS vasculitis patient with a history of hypertension presenting with cough and fever required intubation on day 3 of hospital admission (13).

Nearly all of the patients who were diagnosed with acute myelitis were administered to the hospital due to neurologic symptoms, especially limb weakness. Most of the observations indicated mild flu-like symptoms such as cough and fever at onset (10, 36, 38, 39, 68, 71). Likewise, most of the patients with NMOSD didn't experience respiratory symptoms severe enough to seek medical attention (17, 76). However, various presentations of COVID-19 were still observed, including fever, chills, cough, shortness of breath, and gastrointestinal complications (34, 76). This pattern was similarly seen among patients with optic neuritis while most of the reports indicated that these patients were generally healthy at admission except for visual problems (5, 49, 50, 80).

CT results were usually indicative of pulmonary pneumonia in ADEM patients with COVID-19. In addition, dyspnea and fever were commonly seen in ADEM patients (6, 7, 54, 78, 79), while also some cases reported respiratory failure due to COVID-19 which required intubation (51, 52, 81).

Overall, it seems that the severity of COVID-19 in patients manifesting autoimmune-related neurologic symptoms depends mostly on known factors linked with disease severity in normal patients, such as higher age and concomitant metabolic and heart diseases. Furthermore, the immunosuppressive therapies in these patients play a critical role in further respiratory status.

Treatment and management of patients with CNS autoimmune diseases during COVID-19 pandemic

While previous studies suggested that corticostreids should be prescribed with caution in this patients, recent investigations revealed that these patients should receive corticosteroids due to possible benefits (82-84). These patients could be administered with intravenous human immunoglobulins (IVIG), plasma exchange (PLEX), and immunotherapy if possible (85). Based on Vaschetto et al. study, IVIG and thereafter prescription of methylprednisolone improved cerebral nervous system vasculitis in a COVID-19 patient (13). Also, in Munz et al. report, methylprednisolone was administered due to the absence of active infection and persistent symptoms in COVID-19 patients with acute transverse myelitis after SARS-CoV-2 infection, resulting in rapid improvement (10). Practitioners should notice that moderate steroid therapy should be done while considering SARS-CoV-2 elimination. Based on a case series of para-infection anti-GD2/GD3 IgM myelitis related to COVID-19 infection, administration of corticosteroids, immunoglobulins, PLEX, and rituximab could be beneficial in acute transverse myelitis (10). It should be considered that corticosteroids should be used as soon as possible the active infection is eliminated. If corticosteroid treatment fails, PLEX can be the second option in this population (33). Reports of AE due to COVID-19 mainly treated with methylprednisolone and IVIG (4, 30, 67). These patients are also administered anti-seizure medications such as levetiracetam, clonazepam, and intravenous valproate sodium (11). In addition, other medications such as acyclovir, as an anti-viral drug, sertraline, and risperidone as medications for mood and mental disorders (30, 67). As we discussed, there are few cases of NMOSD secondary to COVID-19 infection, but intravenous methylprednisolone seems to be a good choice in these patients and leading to a significant improvement according to Naomi et al. study (34). Furthermore, another study used IVIG to decrease the risk of prophylaxis for deep vein thrombosis and thromboembolism due to COVID-19 infection. Also, they used combination therapies such as oseltamivir, chloroquine, paracetamol, azithromycin, ceftriaxone, and then meropenem, ciprofloxacin, and teicoplanin (18). According to our knowledge there are only two cases reported with CNS vasculitis due to COVID-19 infection and only one of them described the therapeutic approach which included IVIG and metilprednisolone (13).

Demographical features, comorbidities, and risk factors

Regarding the demographic factors of patients presented with autoimmune encephalitis as a possible complication of COVID-19, the mean age of patients was 59.4 years (86). Also, 71.7% of patients had at least one comorbidity such as hypertension (45.5%) followed by hyperlipidemia (24%) and diabetes mellitus (16%) (86). Anti-NMDAR encephalitis is the most common type of autoimmune encephalitis regardless of COVID-19 infection (87), while reports of anti-NMDAR encephalitis were with no limitation of age, affecting 23 months (28) old patient to 50 years old patients (32) and mostly presented with acute psychosis and to lesser extend acute ataxia (88). According to a recent systematic review of 5 definite cases of COVID-19 related autoimmune Limbic encephalitis, 3 subjects were women and 2 were men with a mean age of 73.8 years (ranged 66 to 80 years) (64). Based on our search, autoimmune encephalitis presenting as NORSE seems to be more prevalent in elderly men but there is no documented evidence for this hypothesis (29, 59).

In non-pandemic conditions, NMOSD affects 0.5-10 people per 100.000, mostly in the 4th - 5th decade of their life, and also it seems to be more frequent in females (89). During the current pandemic, although there are reports of cases without prior risk factors, patients with preexisting autoimmune disease especially Sjögren's syndrome, and patients with a history of any type of malignancy are more susceptible to developing NMOSD (34). Also, Patients with an increased expanded Disability Status Scale (EDSS), higher age, and also patients with longer duration of disease onset had poorer prognosis and more need for ICU care (90).

To our knowledge, there were limited cases of CNS vasculitis, but reports were mostly observed in elderlies with dominance in men (91). Cardiovascular and metabolic risk factors including the history of hypertension, diabetes mellitus, hypercholesterolemia, and ischemic heart disease may be present in these patients, which may be due to higher age in these patients (42, 92).

As patients with MS are generally younger and also dominantly female, it is expected that they are at lower risks of hospitalization but according to a recent meta-analysis, the hospitalization rate due to COVID-19 is higher among MS patients, with a rate of 10% (91). Similar to the normal population studies have shown higher age, having at least 1 comorbidity and male sex is associated with a higher hospitalization rate (93). There are few reports of MS exacerbation and development due to COVID-19 infection, so the demographical features of MS patients with COVID-19 cannot be defined by previous investigations.

Conclusion

In this study, we aimed to review the overall prevalence, management, risk factors, and potential pathways of several ADs including MS, AE, myelitis, CNS vasculitis, NMOSD, optic neuritis, and ADEM secondary to COVID-19 infection. Symptoms of these diseases vary from main drowsiness, delirium, and motor deficits in ADEM, MS, and AE and also visual impairment, and sensory problems in NMOSD and TM patients. Furthermore, there was a higher number of NMOSD cases secondary to COVID-19 infection compared to other CNS ADs. However, there are several limitations in our study such as lack of access to all cases because not all patients were reported before and remained unknown.

On the other hand, several diseases such as optic neuritis and CNS vasculitis were very rarely reported due to COVID-19 in previous studies. The severity of COVID-19 symptoms was

also different from disease to disease. Cases with NMOSD and TM experienced almost no significant respiratory stress and the main cause of hospitalization in these groups was due to the neurologic problems and limb weaknesses while subjects with ADEM administrated to the hospital mainly because of respiratory failure and shortness of breath. Based on the previous studies moderate corticosteroid therapy or other medication such as IVIG and PLEX is suggested for the treatment of CNS ADs in the COVID patients.

Current shreds of evidence demonstrated that CNS ADs can occur due to COVID-19 infection and the health care system should attention to CNS ADs as a complication of COVID-19. While recent investigation introduces neurological manifestation as a COVID-19 complication, it seems that ADs might be at the top of the list due to the potential immune pathways and autoimmune nature of these diseases. However, further investigations are strongly needed to confirm these findings.

Deceleration

Funding

We do not have any financial support for this study.

Conflict of interest

The author declares no conflict of interest regarding the publication of this paper.

Ethical approval

Not applicable

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

This manuscript has been approved for publication by all authors.

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