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LEADING TOPIC

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COVID-19 and autoimmune diseases of the nervous system — an update

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ABSTRACT

Introduction. Due to a similar pathomechanism, COVID-19 infection may significantly affect the course of autoimmune diseases (AIDs). In our review, we aimed to assess the severity of SARS-CoV-2 infection, response to treatment, and the impact of COVID-19 infection on the course of the underlying disease in patients with neuroimmune diseases.

State of the art. In the time of the COVID-19 pandemic, it was important to determine the influence of COVID-19 infection on the course of autoimmune diseases due to the weakened immune system and immunosuppressive therapies.

Clinical implications. Many reports have indicated that in patients with AIDs, the existence of the disease is not associated with a worse prognosis in the course of the viral infection. Patients in advanced stages of the disease, elderly patients, and those with comorbidities are at risk of more frequent hospitalisations and higher mortality in the course of COVID-19. Moreover, some drugs used in AIDs have been tested for their efficacy in SARS-CoV-2 infection. Episodes of newly diagnosed myasthenia gravis, Guillain-Barré syndrome, acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica spectrum disorder (NMOSD) secondary to COVID-19 or vaccination have also been reported. Vaccination against this pathogen is highly recommended in most patients with AIDs.

Future directions. Despite many studies on the association between COVID-19 and neuroimmune diseases, more specific data is needed. The approach to patients with AIDs should be individual, since many issues remain unresolved despite the long-lasting pandemic.

Key words: COVID-19, SARS-CoV-2, AIDs, neuroimmune diseases

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Introduction

Coronavirus Disease 2019 (COVID-19) is a contagious disorder caused by the novel coronavirus which belongs to the Betacoronavirus genera [1]. The first case of unusual viral pneumonia caused by SARS-CoV-2 was described in Wuhan, China, in December 2019. Despite the restrictions, a growing number of infections that spread worldwide resulted in the declaration of a pandemic within three months [1]. To date (October 2022), 615 million laboratory-confirmed cases of the disease and 6.5 million deaths have been reported worldwide [2].

Autoimmune diseases (AIDs) are caused by impairment of the immune system, which results in the production of antibodies against one's own tissues. This leads to clinical damage or impairment of their function [3]. At the time of the COVID-19 pandemic, patients affected by AIDs may be exposed to a more severe course of infection due to the failure of the immune system. Moreover, the use of immunosuppressants may also increase susceptibility to COVID-19.

We reviewed the literature to describe the impact of the pandemic on the course of neuroimmune diseases. The aim of our study was to assess the severity of COVID-19, the response

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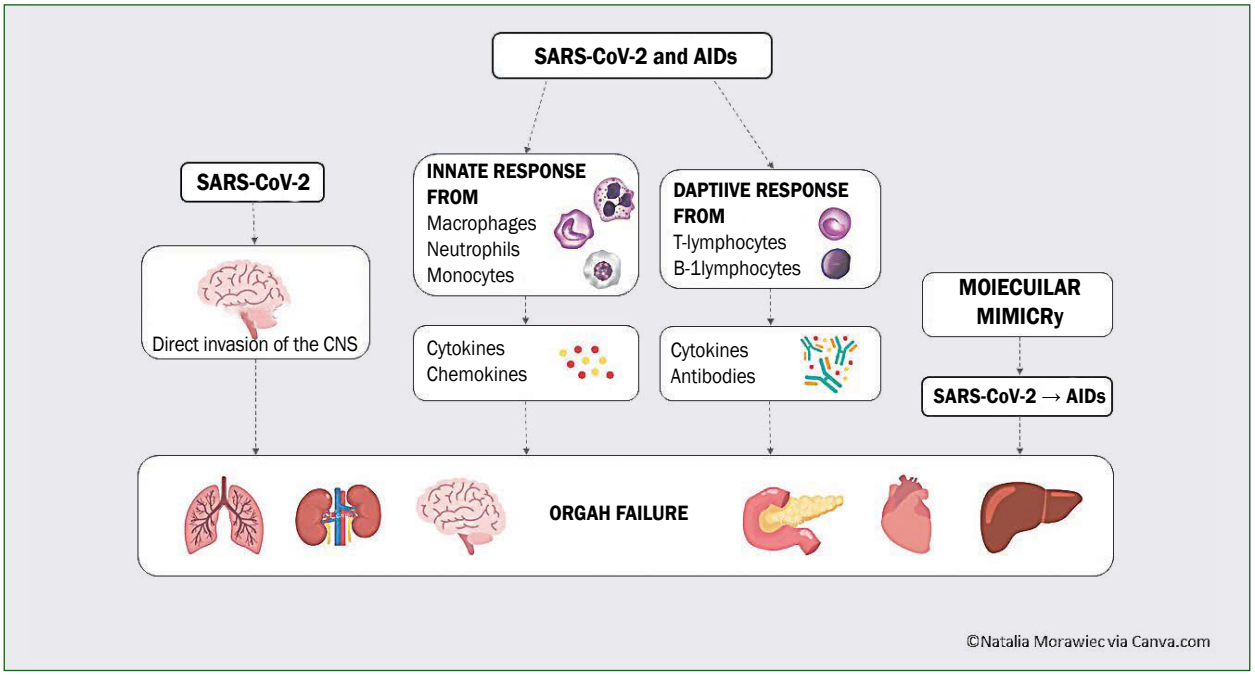

Figure 1. Similarities in pathophysiology of neuroimmune diseases and SARS-CoV-2. Both COVID-19 and AIDs activate immune system, which results in cytokine and antibody overproduction. Another mechanism of viral penetration is direct invasion of central nervous system by SARS-CoV-2. Due to molecular mimicry in cases with COVID-19, production of antibodies may lead to *de novo* occurrence of AIDs. AIDs — autoimmune diseases; CNS — central nervous system; IS – immune system

to treatment, and the impact of COVID-19 infection on the course of the underlying diseases in patients with autoimmune diseases of the nervous system.

Material and methods

This paper assesses and compares research on autoimmune diseases of the nervous system at the time of the COVID-19 pandemic. We reviewed the systematic literature, including our own papers on selected neuroimmune diseases and COVID-19. We searched PubMed, Scopus and Google Scholar using the phrases: 'COVID-19' and 'SARS-CoV-2' together with 'autoimmune', 'neuroimmune', 'multiple sclerosis', 'NMOSD', 'myasthenia gravis', 'Guillain-Barré syndrome' and 'ADEM'. As a result, relevant articles were selected. All the papers included in this review were published between 2020 and 2022.

Similarities in pathogenesis of SARS-CoV-2 infection and neuroimmune diseases

In AIDs and in SARS-CoV-2 infection, the inflammatory process affects various locations. Symptoms can occur in many organs and systems, such as the cardiovascular system, nervous system, lungs, kidneys, skin, or digestive tract [4]. Excessive production of cytokines and the activation of immune cells lead to the production of antibodies and organ failure in AIDs and SARS-CoV-2 infection. Overproduction of the proinflammatory molecules (IL-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, CCL2) results in cytokine storm [5]. Another similarity between AIDs and COVID-19 is that cells of the innate immune response (macrophages, monocytes, mast cells, neutrophils) are over-activated. Furthermore, dysregulation between the levels of B-cells and T-cells has been reported with reduced T-cell levels [4].

Furthermore, in some patients with COVID-19, the presence of autoantibodies characteristic of neuroimmune diseases has been found. Halpert and Shoenfeld reported infected cases with antibodies characteristic of Guillain-Barré syndrome (ANA, antinuclear antibodies), Miller-Fisher syndrome (aCL, anti-cardiolipin antibodies), neuromyelitis optica [anti-phosphatidylserine antibodies (IgM/IgG)], NMDA-receptor encephalitis [antiannexin V (IgM/IgG)], and myasthenia gravis (anti-GD1b antibodies) [6]. AIDs can also occur secondarily to COVID-19. Infection with the SARS-CoV-2 virus can lead to the activation of autoimmune processes due to molecular mimicry [7]. There is another hypothesis of direct viral invasion of the central nervous system. PCR-positive cerebrospinal fluid (present in several cases) seems to confirm this [8]. The above mechanisms are shown in Figure 1.

Course of neuroimmune disorders and impact on SARS-CoV-2 infection

In our review, we have selected the most common AIDs of the nervous system, which are presented below. Detailed information on the study groups, the course of the infection, treatment and clinical outcomes is given in Table 1.

Table 1. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
MS	Castillo Álvarez et al. [11]	Spain	N: 330 Female %: 75 Mean age: 47.91 Mean EDSS: 1.92	Positive PCR: 9 Serology: 3	Cough, fever, pharyngeal pain, myalgia, asthenia, headache, dyspnoea and anosmia	Interferon beta-1a: 2 (16.66%) Dimethyl fumarate: 2 (16.66%) Teriflunomide: 2 (16.66%) Fingolimod: 1 (8.33%) Cladribine: 1 (8.33%) Alemtuzumab: 1 (8.33%) No treatment: 3 (25%)	A more severe course of SARS-CoV-2 infection required hospitalisation in MS group compared to healthy controls. Risk of infection was twice as high as in general population. Mortality rate of COVID-19 in MS group was 11.1%
MS	Louapre et al. [12]	France	N: 347 Female %: 71.75 Mean age: 44.6 Mean EDSS: 2.0	Positive PCR: 146 Ground-glass opacity on CT scan: 62	Asthenia, fever, cough, anosmia, ageusia, headache, dyspnoea	Interferon beta: 20 (5.8%) Glatiramer: 33 (9.5%) Teriflunomide: 33 (9.5%) Dimethyl fumarate: 35 (10.1%) Natalizumab: 57 (16.4%) Fingolimod: 42 (12.1%) Ocrelizumab: 38 (11.0%) Rituximab: 17 (4.9%) Cladribine: 3 (0.9%) Alemtuzumab: 1 (0.3%) Other: 5 (1.4%) No treatment: 63 (18.2%)	Need for hospitalisation in older patients and subjects with higher EDSS. A more severe course of COVID-19 (severity score of 3 or more) correlated with lymphopenia. Mortality rate of COVID-19 in MS group was 3.5%
MS	Crescenzo et al. [16]	Italy	N: 1,034 Female %: 73.98 Mean age: 49 Mean EDSS: 4.0	Positive PCR: 11 Suspected: 18	Fever, dyspnoea	Dimethyl fumarate: 12/29 (41.4%) Fingolimod: 4/29 (13.8%) Natalizumab: 2/29 (6.9%) Ocrelizumab: 7/29 (24.1%) Teriflunomide: 2/29 (6.9%) Azathioprine: 1/29 (3.4%) No treatment: 1/29 (3.4%)	Need for hospitalisation in two male patients on FG and DMF. No deaths secondary to COVID-19 were reported in study group. No connection between DMT and a more severe course of infection. No connection between immunosuppression and a more severe course of infection
MS	Barzegar et al. [19]	Iran	N: 543 Female %: 81.22 Mean age: 35.28 Mean EDSS: 0.0	Positive PCR: 2 Ground-glass opacity on CT scan: 7	Fever, dyspnoea, sore throat, diarrhoea, cough, anosmia	Interferon beta: 296 (54.4%) Glatiramer acetate: 35 (6.5%) Fingolimod: 55 (10.1%) Dimethyl fumarate: 27 (5.1%) Teriflunomide: 20 (3.7%) Rituximab: 42 (7.7%) Natalizumab: 12 (2.2%) No treatment: 56 (10.3%)	A severe course of infection in fingolimod-treated patient and a critical course in one patient on rituximab

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Table 1. cont. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
MS	Vogel et al. [21]	USA	N: 1,019 Female %: 79.50% Mean age: 54.2 Mean EDSS: 2.76	Positive PCR: 7	Fever, dry cough, dysgeusia, anosmia	Glatiramer acetate: 83 (8.14%) Interferon beta-1: 44 (4.32%) Peginterferon beta-1a: 7 (< 1%) Fingolimod: 81 (7.95%) Siponimod: 8 (< 1%) Dimethyl fumarate: 87 (8.54%) Diroximel fumarate: 3 (< 1%) Teriflunomide: 45 (4.42%) Cladribine: 10 (< 1%) Natalizumab: 67 (6.58%) Rituximab: 38 (3.73%) Ocrelizumab: 238 (23.36%) Alemtuzumab: 7 (< 1%) Other: 10 (< 1%) No treatment: 270 (26.50%)	No need for hospitalisation and no deaths in study group. Thirty eight patients were exposed to COVID-19. Delay in drug administration in 98 (10%) patients and need to postpone medical visits in 64% due to COVID-19
MS and NMOSD	Alonso et al. [18]	Latin America (15 countries)	N: 16 Female %: 71.7 Mean age: 41 Mean EDSS: 4	Suspected: 27 Confirmed: 118	NI	**MS:** Interferon: 21 (16.2%) Glatiramer acetate: 2 (1.5%) Fingolimod: 30 (23.2%) Dimethyl fumarate: 13 (10%) Teriflunomide: 12 (9.3%) Cladribine: 4 (3.1%) Natalizumab: 8 (6.2%) Ocrelizumab: 10 (7.7%) Alemtuzumab: 5 (3.8%) Rituximab: 12 (9.3%) No treatment: 12 (9.3%) **NMOSD:** Azathioprine: 2 (12.5%) Mofetil mycophenolate: 2 (12.5%) Rituximab: 11 (68.7%)	**MS:** 15% of MS group required hospitalisation, particularly elderly patients. No deaths secondary to COVID-19 were reported in study population **NMOSD:** 56.25% of patients required hospitalisation. Mortality rate of COVID-19 was 31.2% in NMOSD group (all treated with rituximab)

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Table 1 cont. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
NMOSD	Sahraian et al. [25]	Iran	N: 130 Female %: 83.15 Mean age: 37.55	Positive PCR: 3 Ground-glass opacity on CT scan: 2	Fever, dyspnoea, myalgias, gastrointestinal complications, fatigue, vertigo, headache, odynophagia	Azathioprine: 22 (16.9%) Rituximab: 94 (72.3%) Mycophenolate mofetil: 2 (1.5%) Prednisolone: 1 (0.8%) Mitoxantrone: 1 (0.8%) Azathioprine & Prednisolone: 2 (1.5%) Rituximab & Mycophenolate mofetil: 1 (0.8%) Rituximab & Cyclophosphamide: 2 (1.5%)	Occurrence of COVID-19 was reported only in rituximab group. Three patients required hospitalisation. Infection rate in NMOSD patients was same as in general population. Gastrointestinal manifestations of infection were reported in 40% of subjects
NMOSD	Fan et al. [10]	China	N: 3,060 Female %: NI Mean age: NI Mean EDSS: NI	Confirmed: 2	NI	Methylprednisolone: 795 (25.98%) Azathioprine: 405 (13.24%) Mycophenolate mofetil: 832 (27.19%) Tacrolimus: 403 (13.17%) Rituximab: 381 (12.45%) Tocilizumab: 62 (2.03%) Cyclophosphamide: 39 (1.27%)	No increased risk of COVID-19 infection was found in study group (two confirmed cases). Successful recovery from viral pneumonia was reported in both patients
NMOSD	Yin et al. [23]	China	N: 535 Female %: 88.04 Mean age: 43.8 Mean EDSS: 1.5	Confirmed: 0	NI	Mycophenolate mofetil: 381 (71.2%) Azathioprine: 71 (13.27%) Other immunosuppressants: 34 (6.36%)	Treatment disruptions due to pandemic resulted in more relapses of NMOSD. No increased risk of COVID-19 infection was reported in study group (no confirmed cases).
MG	Tuncer et al. [32]	Turkey	N: 140 Female %: NI Mean age: NI	Positive PCR: 19	Fever, muscle pain, fatigue, anosmia	Prednisolone & IVIg: 1/19 (5.26%) Azathioprine: 1/19 (5.26%) Prednisolone & Azathioprine: 7/19 (36.84%) Prednisolone & Rituximab: 1/19 (5.26%) Prednisolone: 4/19 (21.05%) Prednisolone & Mycophenolate mofetil: 1/19 (5.26%) No treatment: 4/19 (21.05%)	A mild course of COVID-19 was observed in most MG patients. Two deaths secondary to SARS-CoV-2 infection were found in study group. Need for hospitalisation in six patients with MG
MG	Rodrigues et al. [34]	Brazil	N: 8 Female %: 87.5 Mean age: 47.13	Positive PCR: 8	Fever, shivering, odynophagia, headache, dyspnoea, dysphagia, dysphonia, post-prandial cough, bilateral ptosis, diplopia	Prednisone & Azathioprine & Pyridostigmine: 3 (37.5%) Pyridostigmine: 1 (12.5%) Prednisone & Methotrexate & Pyridostigmine: 1 (12.5%) Prednisone & Pyridostigmine & Rituximab: 1 (12.5%) No treatment: 2 (25%)	Exacerbation or myasthenic crisis in eight patients. Six patients required mechanical ventilation. In-hospital mortality was 25% and 37.5% in short-term follow-up

Table 1 cont. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
MG	Businaro et al. [31]	Italy	N: 162 Female %: 40.1 Mean age: 66	Positive PCR: 3 Suspected: 8	Ptosis, mild-to-moderate proximal and distal weakness in upper and lower limbs, diplopia, tongue weakness, neck weakness, dysphagia, facial muscle weakness	Prednisone < 10 mg/d: 31 (19.1%) Prednisone > 10 mg/d: 39 (24.1%) Azathioprine: 47 (29.0%) Other immunosuppressants: 7 (4.3%) No immunosuppressants: 63 (38.9%) Treatment with IVIg/PlEx: 26 (16.0%)	Mortality secondary to COVID-19 was found in two elderly patients. Exacerbation of MG during infection was reported in one patient
MG	Camelo-Filho et al. [35]	Brazil	N: 15 Female %: 60 Mean age: 45.22	Positive PCR: 15	Dyspnoea, fever, cough, myalgia	Prednisone: 4 (26.67%) Prednisone & Azathioprine & IVIg: 1 (6.67%) Prednisone & Methotrexate: 2 (13.33%) Prednisone & Cyclosporin: 1 (6.67%) Prednisone & Azathioprine: 4 (26.67%) No treatment: 1 (6.67%)	Exacerbation of MG or use of mechanical ventilation was reported in most patients from study group. 86.7% of patients needed hospitalisation in ICU. Death secondary to COVID-19 was reported in four patients
MG	Rzepiński et al. [33]	Poland	N: 30 Female %: 83.33 Mean age: 42.3	Positive PCR: 10	Fever, chills, myalgia, headache, cough, fatigue, ageusia, anosmia, dyspnoea	Plasma exchange: 4 (13.33 %) IVIg: 6 (20%) Cholinergic therapy: 29 (96.7%) Corticosteroids: 20 (66.7%) Non-steroidal immunosuppressants: 15 (50%)	11 patients needed hospitalisation. MG exacerbation due to COVID-19 in three patients. No deaths secondary to COVID-19 in study group
GBS	Filosto et al. [40]	Italy	N: 34 Female %: 26.67 Mean age: 59.2	PCR-positive/ seropositive: 30	Fever, cough, dyspnoea, dysgeusia, anosmia, gastrointestinal symptoms, paresis, facial diplegia with mild distal weakness, pharyngeal–cervical–brachial weakness, sensory impairment	Plasma exchange: 2/30 (6.67%) IVIg: 25/30 (83.33%) No treatment: 3/30 (10%)	More frequent admission to ICU among GBS COVID-19-positive patients. Need for mechanical ventilation in 25 patients. 90% of COVID-19-positive subjects and 100% of negative cases with classic form of GBS. A worse course of GBS was reported in COVID-19 group. No deaths secondary to COVID-19 were reported in study group
GBS	Rahimi et al. [44]	Multicentre	N: 31 Female %: 45.17 Mean age: 57.26	Positive PCR: 31	Paresthesia in feet and hands, symmetric weakness in lower limbs, facial palsy, acute proximal tetraparesis, gait difficulties, and root-type pain in all four limbs	NI	Need for hospitalisation in five patients with GBS. GBS secondary to COVID-19 was found mostly in elderly men
GBS	Gittermann et al. [41]	Multicentre	N: 30 Female %: 36.67 Mean age: 59.8	Positive PCR: 28 Seropositivity: 2	Fever, pneumonia, paresthesia, hyperesthesia and symmetrical weakness of limbs, areflexia, anosmia, ageusia, bilateral masseter weakness, paralysis of hypoglossal nerve, myalgia, diarrhoea, etc	IVIg: 27 (90%) Antiretroviral therapy: 8 (27%) Hydroxychloroquine: 12 (40%) Other (hydroxychloroquine, prednisone, and antiretroviral therapy but not immunoglobulins): NI	Older age and male sex positively correlated with occurrence of GBS. No deaths secondary to COVID-19 were reported in study group

Table 1 cont. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
GBS following vaccination	García-Grimshaw et al. [85]	Mexico	N: 7 Female %: Mean age: 51.71	NA	NA	IVIg: 7 (100%)	Incidence of GBS in studied population rated as 0.18/100,000. All cases of GBS occurred after first dose of BNT162b2 mRNA vaccine. No cases were reported after second dose
GBS following vaccination	Shapiro et al. [79]	Israel	N: 702 Female %: 48 Mean age: 53	NA	NA	Plasmapheresis: 1 (0.14%)	Forty eight patients had visited emergency department. Need for hospitalisation only in one patient (relapse of previous syndrome)
MFS following vaccination	Siddiqi et al. [86]	Pakistan	N: 1 (case report) Male Age: 53	NA	NA	IVIg Pregabalin	Case of MFS following first dose of Sinovac–Coronavac COVID-19 vaccine. Complete resolution of symptoms 10 weeks after discharge
ADEM	Zelada-Ríos et al. [48]	Multicentre	N: 20 Female %: 25 Mean age: 49.8	Positive PCR: 20 Seropositivity: 1	Pyramidal signs, brainstem signs, cerebellar signs, seizures, peripheral nerve compromise	Dexamethasone: 2 (10%) Methylprednisolone: 5 (25%) IVIg: 1 (5%) Methylprednisolone & IVIg: 5 (25%) IVIg & Tocilizumab: 1 (5%) Supportive: 1 (5%) NI: 5 (25%)	66.7% with a severe course of infection. One positive PCR for COVID-19 in CSF. Occurrence of encephalopathy in most cases. A fully favourable outcome was reported in 7/9 patients in follow-up, while a partially favourable outcome was found in 2/9 patients. Two deaths secondary to COVID-19 were reported in study group
ADEM	Manzano et al. [49]	Multicentre	N: 46 Female %: 37 Mean age: 49.5	Positive PCR: 34 Seropositivity: 6 Method not specified: 2 Suspected: 4	Seizures, encephalopathy, aphasia, focal motor and sensory deficits, cranial nerve deficits, cerebellar deficits, urinary retention, autonomic instability	Methylprednisolone i.v.: 24 (52%) Oral steroids: 10 (22%) IVIg: 2 (4%) IVIg & Methylprednisolone & PlEx: 11 (24%) Plasmapheresis: 2 (4%) Rituximab: 1 (2%) Ocrelizumab: 1 (2%) Cyclophosphamide: 1 (2%) Neurosurgical intervention: 2 (4%) Mannitol: 1 (2%) Supportive care: 9 (20%) No treatment: 5 (11%)	Need for ICU admission in 67% of cases. Haemorrhage on brain MRI in 42% of cases. Non-inflammatory CSF in 30% of patients. Nine deaths secondary to COVID-19 were reported in study group

ADEM — acute disseminated encephalomyelitis; AE — autoimmune encephalitis; AHLE — acute haemorrhagic leukoencephalitis; CT — computed tomography; DMF — dimethyl fumarate; DMT — disease-modifying therapy; FG — fingolimod; GBS — Guillain–Barré Syndrome; ICU — Intensive Care Unit; IVIg — intravenous immunoglobulin; LD — limited data; MFS — Miller–Fisher Syndrome; MG — myasthenia gravis; MS — multiple sclerosis; NA — not applicable; NMOSD — Neuromyelitis Optica Spectrum Disorder; NI — no information; N — number of patients; PlEx — plasma exchange

Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease that affects the central nervous system. It is usually diagnosed between 20 and 40 years of age. It is characterised by remissions and exacerbations, which gradually lead to disability [9]. Due to the autoimmune nature of the disease and the immunomodulatory therapies, it was important to determine the impact of COVID-19 on the course of MS. In most studies, the existence of MS has not been shown to significantly increase the risk of COVID-19 infection [10]. However, some reports have indicated that MS patients are more susceptible to it [11]. Older obese patients and subjects with higher disability scores were found to be more at risk of a worse course of SARS-CoV-2 [12]. However, in some cases, younger, less disabled patients could be more vulnerable because of their more frequent social interactions [13]. COVID-19 infection can also contribute to the exacerbation of the underlying disease. There have been some reports related to COVID-19-induced relapse and failure of the applied treatment due to the viral invasion [8, 9].

Most studies have found no significant correlation between disease-modifying therapy (DMT) and a more severe course of COVID-19 [4, 5, 7]. Alonso et al. showed that patients on rituximab were more at risk of death from SARS-CoV-2 [18]. Additionally, Barzegar et al. [19] demonstrated that one patient who was administered rituximab had a critical course of disease. Some data has suggested that anti-CD20 therapies could contribute to a higher probability of infection and a severe course of COVID-19 [20]. Another cross-sectional study showed that natalizumab was related to a higher risk of infection. Treatment in hospital settings has also been reported to be connected to higher susceptibility as opposed to home-based drug administration [21]. However, all these findings should be interpreted with caution because of the different conclusions made by the various authors.

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an inflammatory demyelinating disease affecting the optic nerves and the spinal cord. It is characterised by the presence of IgG autoantibodies against aquaporin 4 (AQP4) [22]. Due to increased susceptibility to bacterial and viral infections following immunosuppressive therapies, it was crucial to determine the impact of SARS-CoV-2 on the course of the disease. Several studies found no increased risk of infection due to NMOSD [4, 14]. In their meta-analysis, Barzegar et al. [24] showed that the prevalence of COVID-19 in patients with NMOSD was 1.2%, while the mortality rates ranged from 0 to 31.3%. In terms of immunosuppressive treatment, no risk of drug administration has been reported during the pandemic. However, patients should follow the restrictions and observe social distancing [10].

Studies showed that the administration of rituximab and the presence of comorbidities could be risk factors for COVID-19 [24]. Studies also found that patients on rituximab were more likely to develop gastrointestinal manifestations of COVID-19 infection and a worse course of the disease that required hospitalisation (60%) [25]. Research showed an increased risk of relapse during the pandemic, not only due to COVID-19 infection, but also to the accompanying chronic stress [23].

There are some reports on NMOSD following COVID-19 infection or vaccination. Based on 11 reports, Mirmosayyeb et al. [26] showed that a first episode of NMOSD could occur after SARS-CoV-2 infection. Furthermore, some cases of NMOSD with the presence of MRI lesions and AQP4 IgG after COVID-19 vaccination have also been reported [14–16]. Despite the rising concerns, resolving this issue would require further investigation and long-term surveillance of such patients.

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction. It is characterised by the presence of IgG antibodies against the nicotinic acetylcholine receptor (nAChR) [30]. Patients with MG are more susceptible to SARS-CoV-2, particularly those with a higher Myasthenia Gravis Foundation of America (MGFA) clinical class [31]. Well-controlled MG and the absence of comorbidities has been shown to correlate positively with a milder course of COVID-19 infection [32]. Interestingly, according to a Polish study, COVID-19 infection does not necessarily worsen MG severity as assessed by the MGFA classification [33]. Exacerbation of the disease caused by COVID-19 occurred in 10–15% of patients with MG. Rodrigues et al. described eight patients with MG exacerbation and myasthenic crisis during the viral infection. The main risk factors for a worse prognosis and death included long-term corticosteroid use, older age, cancer, and rituximab use [34]. Patients with MG could be more vulnerable to a severe course of COVID-19. However, there is some evidence that immunosuppressive therapy may have a protective effect [35]. The type of treatment does not influence the occurrence of SARS-CoV-2. Patients should continue their therapy during the pandemic [31]. Studies have shown that azathioprine, mycophenolate mofetil, and cyclophosphamide do not significantly affect the outcomes. Large doses of corticosteroids and the administration of rituximab could be related to higher mortality rates [34]. However, corticosteroids may actually play a protective effect in moderate and severe COVID-19 [32].

SARS-CoV-2 infection may not only exacerbate the disease, but also contribute to the development of a new episode of MG. This unexpected neurological manifestation suggests that the virus could induce the production of antibodies. However, further studies are warranted in this regard [26, 27].

Guillain-Barré syndrome

Guillain-Barré Syndrome (GBS) belongs to the most common acquired demyelinating polyneuropathies. The exact cause of the disease is unknown. Nerve damage is associated with autoimmune processes [38]. The onset of GBS is usually preceded by an infection, mostly of the lower respiratory tract.

The pathogens that could be aetiological factors of GBS include *Campylobacter jejuni*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, the *Zika* virus, etc. Since 2020, new cases of GBS secondary to SARS-CoV-2 have been reported [39].

Filosto et al. [40] observed a significant increase in GBS during the pandemic. Moreover, COVID-19-associated GBS had a more severe course than non-COVID-19 GBS. The first manifestation of GBS usually occurs 5–21 days after infection. The highest incidence is among older men (aged 60+ years), yet the mean age before the pandemic was 40 years [41]. The red flags that may indicate the occurrence of GBS in the course of infection include anosmia, ageusia, cranial neuropathies and lymphocytopenia. Early diagnosis and the initiation of treatment are essential. The primary therapeutic methods are IVIg and plasma exchange [42]. In COVID-19-related and non-related GBS, the response to treatment is similar [40]. Li et al. [43] made a systematic review describing patients with Miller-Fisher syndrome, a variant of GBS, after SARS-CoV-2 infection. These unusual manifestations of the viral infection underline the importance of follow-up and neurological examination in COVID-19 patients [44].

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a demyelinating autoimmune disease with sudden episodes of inflammation in the brain and the spinal cord [45]. It can occur at any age, although most cases are seen in children [46]. ADEM is usually triggered by infection or vaccination. There is limited data on the COVID-19 course in patients with pre-existing ADEM. Hussein et al. [47] showed a case of Coxsackie-induced ADEM exacerbated by SARS-CoV-2 infection. Treatment with steroids and plasmapheresis resulted in a favourable outcome. Zelada-Ríos et al. [48] published a systematic synthesis of worldwide cases of ADEM secondary to COVID-19 (Tab. 1). They found that the prevalence of this condition was higher among adult men than in children. The mean time from the onset of infection to the development of ADEM was 23.2 days (4–60 days). Another meta-analysis showed the existence of acute haemorrhagic leukoencephalitis (AHLE) in the course of SARS-CoV-2 infection, with high rates of brain haemorrhage on MRI (30%) [49]. In most patients, steroid therapy, IVIg and plasmapheresis are effective methods of treatment [35,38]. Unfortunately, ADEM in the course of COVID-19 contributes to more frequent hospitalisation in intensive care units, higher mortality, and long-term neurological deficits [50].

Other autoimmune diseases

Cases of other neuroimmune disorders secondary to COVID-19 have also been reported. Autoimmune encephalitis is brain inflammation with the production of antibodies against self-antigens [51]. Anti-NMDAR, anti-MOG, anti-GAD, anti-GD1a and anti-CASPR2 are significant molecules that play a role in its origin [52]. There is limited data on AE and COVID-19. Payus et al. [8] demonstrated that most COVID-19-associated cases (77%) occurred during the acute phase of the infection. Thirty percent of patients presented with neurological symptoms before developing fever and respiratory symptoms. Apart from typical infectious symptoms, the most common presentations are as follows: psychomotor agitation, hallucinations, seizure, anxiety, thought disorganisation, persecutory delusions and insomnia [8]. Treatment with corticosteroids, IVIg, plasma exchange and antiseizure medications is effective in most cases. Limbic encephalitis (LE) may be another complication of SARS-CoV-2. This is a form of encephalitis limited to the medial temporal lobes and is caused by autoimmunity [53]. It is characterised by the production of auto-antibodies, such as anti-Hu, anti-Ma2 and anti-NMDAR [54]. It is mainly diagnosed as a paraneoplastic phenomenon. There are some reports of LE associated with SARS-CoV-2 [39–42]. The mean age of patients was 73.8 years (66–80 years), as reported by Pizzanelli et al. The most common symptoms included seizures, neuropsychiatric symptoms, confusion and amnesia. Typical lesions in medial temporal lobes were present on brain MRI. In all described cases, the disease resolved after treatment with corticosteroids, IVIg, or plasma exchange [58].

Effects of treatment of neuroimmune diseases on SARS-CoV-2 infection

The use of immunosuppressants and adhering to the principles of social distancing seem to be safe in most cases, and do not increase susceptibility to COVID-19 infection. Some drugs used in neuroimmune diseases have been tested for their effectiveness in COVID-19 [59].

Glucocorticoids, which are widely used in AIDs, reduce mortality from severe COVID-19. However, some data has indicated that high doses during AID treatment could worsen the prognosis and be associated with a higher risk of hospitalisation and death [60].

In our previous review, we included some immunomodulatory drugs (interferons, teriflunomide and leflunomide) used in MS that were tested in SARS-CoV-2 infection [59]. Rabie et al. [61] showed that the use of teriflunomide in patients with COVID-19 reduced the cytokine storm. Other studies showed that leflunomide, a dihydroorotate dehydrogenase (DHODH) inhibitor, was associated with faster hospital discharge or reduction in C-reactive protein (CRP) levels in COVID-19 cases [61, 62]. IMU-838 is another promising candidate from this group. It has shown antiviral properties in patients infected with SARS-CoV-2 [64]. Yousefi et al. [65] assessed fingolimod as one of the potential drugs that could stop the virus from invading the CNS. However, the above studies did not consider lymphopenia to be a significant indicator in patients. The National Institutes of Health suggests the use of IL-6 inhibitors (tocilizumab, sarilumab and siltuximab) during SARS-CoV-2 infection. IL-6 inhibitors are also in the research phase related to NMOSD. In COVID-19,

they may contribute to the reduction of the cytokine storm [66]. Another meta-analysis showed the efficacy of IVIg in the course of COVID-19 infection [67]. Plasmapheresis is a different method worthy of consideration. Both of them should be used within 14 days of the onset of infection, which may reduce mortality and shorten hospitalisation [68]. A reduction in proinflammatory cytokine levels and the immune response was also observed in patients with acute respiratory distress syndrome (ARDS) after plasmapheresis [69].

However, all these studies have their limitations due to the pandemic's dynamics and the insufficient number of results confirming treatment efficacy. Therefore, further studies are warranted.

COVID-19 vaccination in patients with neuroimmune disorders

There have been concerns raised about the efficacy and safety of vaccines against COVID-19 in patients with AIDs. In MS patients, vaccination did not increase the risk of relapse or vaccine ineffectiveness [70]. Nevertheless, DMTs can significantly affect the development of the humoral response. Kulikowska et al. [71] revealed that vaccination in MS patients treated with dimethyl fumarate, interferon beta and glatiramer acetate significantly induces the production of IgG and IgA against S protein ($p < 0.0001$). Patients treated with the above-mentioned drugs can efficiently produce antibodies against SARS-CoV 2. In the case of therapies with anti-CD20 antibodies, alemtuzumab and natalizumab, it is recommended to plan the vaccination date individually depending on the last drug administration [70]. In fingolimod-treated patients, attention should be paid to the presence of lymphopenia [72]. In NMOSD patients, vaccination is also safe and not associated with disease progression [73]. Patients treated with rituximab showed a poorer response, and could be at risk of infection despite vaccination [74]. In MG cases, vaccination theoretically may cause disease exacerbation, but patients with MGFA I and II should not avoid vaccination [73, 74]. Qualification for vaccination in other cases should be done on an individual basis, bearing in mind that the benefits outweigh the risks in most patients [77]. The occurrence of COVID-19 had a worse effect on MG than vaccine administration [76]. In patients with a previous episode of GBS not associated with COVID-19, vaccination is recommended. However, age and risk factors must be considered [78, 79]. We found no data about the safety or efficacy of SARS-CoV-2 vaccines in patients with a history of ADEM. Some reports have shown cases of MG, GBS, NMOSD and ADEM following vaccination against SARS-CoV-2 [77–81, 84–86]. Nevertheless, this should be interpreted with caution. Only single cases of such phenomena are usually reported. According to Kaulen et al. [81], severe neurological complications after COVID-19 vaccination are extremely rare (< 0.1%).

Conclusions

Overall, the pathogenesis and immune response in AIDs and COVID-19 share many common features. Both are heterogeneous conditions in which immune-mediated mechanisms can lead to multiple organ failure. The main concern for patients with AIDs is whether the infection is associated with a worse prognosis or an exacerbation of the underlying disease.

In most of the above studies, the presence of AIDs did not significantly affect the infection course. In patients with many comorbidities and advanced disease, the need for hospitalisation and the mortality rate may be higher. The approach to patients with AIDs should be individual because many issues remain unresolved despite the long-lasting pandemic. There is a lack of comprehensive research into specific topics.

However, we hope that our review contributes to a better understanding of the connections between neuroimmune diseases and COVID-19.

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