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Immunopathogenesis of viral infections in neurological autoimmune disease

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Abstract

Autoimmune diseases develop due to self-tolerance failure in recognizing self and non-self-antigens. Several factors play a role in inducing autoimmunity, including genetic and environmental elements. Several studies demonstrated the causative role of viruses; however, some studies showed the preventive effect of viruses in the development of autoimmunity. Neurological autoimmune diseases are classified based on the targets of autoantibodies, which target intracellular or extracellular antigens rather than neurons. Several theories have been hypothesized to explain the role of viruses in the pathogenesis of neuroinflammation and autoimmune diseases. This study reviewed the current data on the immunopathogenesis of viruses in autoimmunity of the nervous system.

Keywords Multiple sclerosis, Autoimmunity, Viral infections, Autoimmune reaction

Introduction

The immune system can identify and remove invading pathogens and prevent infection. Self-tolerance is described as a condition of the immune system that is not reactive to the self-antigen. A self-tolerance process is carried out throughout the immune system development, categorized as either central or peripheral tolerance [1]. The breakdown of self-tolerance and an abnormal immune response to self-antigen could result in autoimmune disorders. Many factors, including genetics, age, and environmental factors, have been found to trigger inflammation and autoimmune reactions [1]; however, the exact etiology of several autoimmune diseases is still unknown. Viruses have long been regarded as an important environmental trigger for autoimmune diseases in genetically predisposed patients [2, 3]. They might activate some immunological responses through self-tolerance breakdown, which might overcome the immune regulating systems and induce autoimmune reactions. The most important known mechanisms in developing virus-induced autoimmunity are molecular mimicry between host self-antigens and microbial antigens, epitope spreading, bystander activation, and immortalizing infected B cells. Molecular mimicry plays a critical mechanism responsible for viruses-induced autoimmune disease. Conventionally, molecular mimicry applies to the similarity of antigens between viruses and self-antigens that can be recognized by immune systems and result in cross-reaction to self-antigens and viral antigens. The

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epitope spreading is another main mechanism responsible for the viruses-induced immune reaction in which viral infection results in more discharge of self-antigens and novel autoreactive cells that subsequently target spared self-antigens [4]. However, the exact contributing mechanism is poorly understood. In the recent COVID-19 pandemic, many COVID-19-associated autoimmune disorder cases have drawn particular attention to the neuropathogenesis of viral infection.

Given the increasing evidence suggesting the association between viral infection and autoimmune disorders, and controversial data on the role of viruses in dysregulation of the immune response, herein, we aim to review the current data on the immunopathogenesis of the common viruses in developing nervous system autoimmune disorders.

Methods

PubMed/Medline electronic database was searched using the keywords "Guillain–Barre syndrome", "Myasthenia Gravis", "autoimmune disease", "Multiple sclerosis", "experimental autoimmune encephalitis", "central nervous system", "COVID-19", "HSV-1", "Influenza", "Epstein barre virus", "EBV", "CMV", "Cytomegalovirus", "Zika Virus", and "varicella-zoster virus". We reviewed the English articles with full-text available between January 1, 2000, to March 1, 2022. A total of 1210 articles were retrieved, and 283 articles were included in this study. The inclusion criteria for this narrative review were studies on the role of selected viruses in developing the neurological autoimmune diseases.

Autoimmune diseases of the nervous system

The incidence of autoimmune diseases is estimated to be more than 5 percent in the general population, with an increasing prevalence in recent years [5]. Up to date, About 80 autoimmune disorders have been identified, including nearly 30 neurological autoimmune diseases [6]. Neurological autoimmune diseases are classified based on the targets of autoantibodies, whereas autoantibodies target intracellular or extracellular antigens of the neurons [7]. Antibody-associated autoimmune diseases against intracellular antigens are often associated with underlying malignancy and are defined as paraneoplastic disorders [7]. Mis-response of the immune system to the ectopic neural antigens, which are aberrantly expressed in malignant cells, direct the hypothetical mechanism of these disorders. Previous studies have shown that autoantibodies against intracellular antigens were not in relation to the target antigens and, therefore, are not responsible for disease development. As a result, these patients have an inadequate response to the treatment. In this regard, some studies investigated the mechanism of autoimmune diseases with intracellular antigens revealing that CD8+T cells penetrated the neurons and induced granzyme B and perforin production, ultimately leading to neural degeneration [8].

Autoimmune diseases associated with the autoantibodies against extracellular epitopes, including cell surface and synaptic antigens, are less related to underlying malignancy. Moreover, in contrast to paraneoplastic CNS disorders, they are characterized by good responsiveness to immunosuppression. There is also a more complicated autoantibody expression pattern, mainly exposed during synaptic fusion and reuptake [8].

Viruses-induced neurological autoimmunity

Some theories have been postulated to explain the role of viruses in the pathogenesis of autoimmune diseases; however, the exact mechanism of viruses-induced neurological autoimmune disorders is still unknown. Altogether four main mechanisms were identified for viruses-induced neurological autoimmune disease: molecular mimicry, epitope spreading, bystander activation, and autoantibody production and immortalization of effector B-cells. Molecular mimicry is defined by similar antigens of self-epitopes and pathogen's antigens, resulting in a cross-reactive reaction of B and T cells to the self-antigen that caused autoimmune disease [9]. The innate immune system causes bystander activation. The immune reaction of the innate immune system provides a strong response against pathogens through the massive production of pro-inflammatory cytokines and chemokines. The overactivation of the immune system's exaggerated response against viruses caused a cytokine storm that initiated additional damage to the neurological tissues and produced more self-antigens. The novel self-antigens are further presented by antigen-presenting cells (APCs) to the autoreactive immune cells and thus trigger an in-process autoimmune reaction [10]. Epitope spreading is another possible mechanism involved in viral-induced neurological autoimmune diseases. Further self-antigens are presented upon ongoing damage to self-tissue and infliction caused by viruses, and other immune reactions were induced by autoreactive T cells to the novel self-antigens [11]. Self-antigen autoantibodies and immortalized effector B cells are caused by memory and affect B cells. Alongside the typical autoantibodies, patients with neurological autoimmune disease can be presented with some other autoantibodies in the nervous system tissues. Additionally, immune system memory cells stimulate effector B cells trained against self-antigens and cause continuous long-term autoantibody production against nervous system antigens [12, 13].

In this study, we sought to review the immunopathogenesis of viruses playing a role in the induction of

autoimmunity of the nervous system, especially following the advent of the COVID-19 pandemic.

Cytomegalovirus

Cytomegalovirus (CMV), the linear double-stranded DNA virus, is a member of the *Herpesviridae* family, introduced in 1904. The virus infects 60 − 100% of people in adulthood [14, 15]. The strong interaction between CMV and the immune system has highlighted its role in inducing autoimmune diseases. Increasing evidence has shown the association of CMV infection with rheumatologic diseases such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA), and some neurological disorders. In contrast, there are reports revealing the protective impact of CMV in some autoimmune diseases such as celiac disease [16]. Moreover, there are controversial reports on the association between CMV and MS. While some reports have suggested the association between reactivation of CMV infection and the development or worsening of pre-existing MS, other studies have shown a negative correlation between the development of MS and CMV seropositivity [17].

Following viral penetration, pattern recognition receptors (PRRs) identify the pathogen-associated molecular pattern (PAMP) and the damage-associated molecular pattern (DAMP) of the virus, which induce the immune reaction to the virus [18]. Molecular mimicry is assumed as another responsible mechanism for CMV-induced autoimmunity. An animal model study demonstrated some degree of molecular mimicry between the myelin oligodendrocyte glycoprotein 35–55 (MOG35-55) and one of the CMV peptides [19]. Immunization of mice with MOG35-55 following murine CMV (mCMV) infection induced symptoms similar to the experimental autoimmune encephalomyelitis (EAE) and increased the influx of T cells (Th-1 and Th-17) into the CNS. In contrast, immunization with MOG35-55 without CMV infection was not able to induce EAE [20]. The cross-reactivity of MOG peptide and CMV peptide has also been proven in a non-human model of primate since MOG34–56 specific T cells responded to the human CMV major capsid protein (UL86; 981–1003) [21].

There is also evidence suggesting the association between CMV and CD4 + CD28null T cells. Human studies have shown a direct relationship between the titer of CMV seropositivity and the number of CD4 + CD28 null T cells [22]. In vitro studies have demonstrated that stimulation with CMV enhances the CD4 + CD28 null T cells population, which all contribute to aggravating the symptoms of EAE [22]. In addition, animal and human fetus studies have shown that CMV infection of the CNS induces CD8 + cells, interferon gamma (IFN-γ), and tumor necrosis factor α (TNFα) accumulation in the CNS, leading to CNS inflammation [19]. The mechanism of CMV-induced multiple sclerosis (MS) is given in Fig. 1.

Zika virus

Zika virus is one of the members of the *Flaviviridae* family, with a single-stranded positive-sense RNA genome, which can participate in the development of some central and peripheral nervous system disorders such as Guillain-Barré syndrome (GBS), transverse myelitis (TM), and meningoencephalitis [23, 24]. Although it was shown that Zika virus infection can be presented wide range of neurological manifestations [25], few studies reported detection of Zika virus in patients with MS [26]. It is suggested that zika virus can induce autoimmune reaction against neural cells that can mimic the presentation of MS [27].

Despite the effect of Zika virus in neurodevelopmental process and congenital pathologies are well understood [4, 28], the impact of zika virus on neural process of adults are remained unknown and the mechanisms underlying ZIKV-induced neuropathogenesis are still poorly understood. It was shown that Zika virus can induce demyelinating process and also axonal injury of neuron related to the CNS that can underlie autoimmune disease of CNS [29]. However, murine studies have demonstrated that ZIKV can replicate and affect the CNS cells, stimulate the expression of inflammatory genes such as interleukin-1 (IL-1) and enhance the expression of NLR family pyrin domain containing 3 (NLRP3) and some other genes responsible for oxidative stress [30]. Other studies have shown that Toll-Like Receptor 3 (TLR3), a part of the innate immune system, is involved in the ZIKV-induced neuropathogenesis since inhibition of the TLR3 function reduces the viral replication and decreases the secretion of inflammatory mediators such as IFN-β and IL-6 from immune cells [31]. Notably, IFN-I pathways are activated during viral infection, allowing the expression of hundreds of elements involved in the IFN-stimulated response. ZIKV non-structural protein 5 (NS5) binds and destroys the Signal Transducer and Activator of Transcription 2 (STAT2) via proteasomal degradation, conferring viral resistance to IFN in cell cultures. Inhibition of IFN is the first step of ZIKV pathogenesis. Following IFN hampering, transmembrane proteins activated by IFN are decreased, resulting in elevation of the ZIKV-caused cell death [32]. It should be noted that following viral invasion, the retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs) as viral RNA detectors are responsible for initiating the innate immune response, which the IFN-I mediates. While the ZIKV can inhibit the IFN-I, it can directly activate the RLRs inducing the

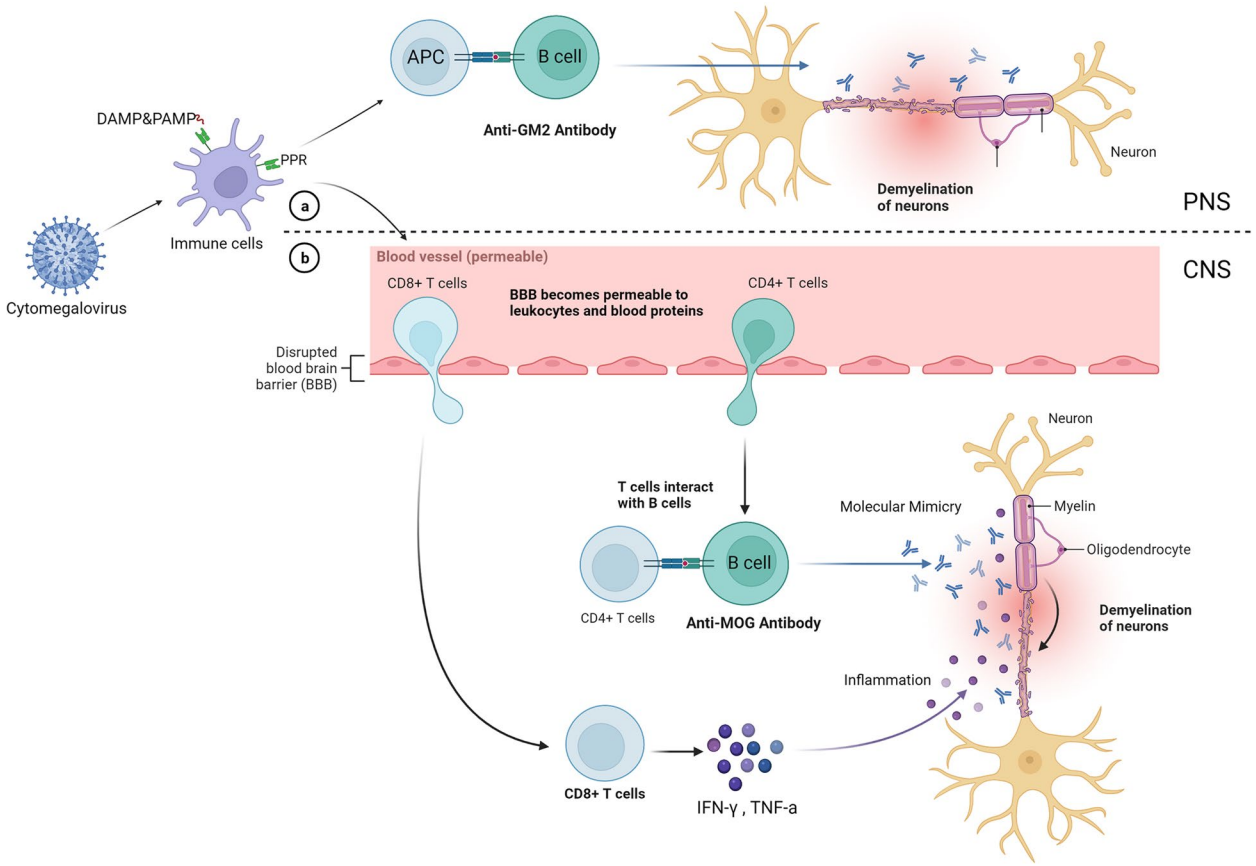

Fig. 1 The mechanism of CMV-induced multiple sclerosis. Immune reaction against the CMV induces autoantibody productions. CMV infection is also associated with a T-cell influx to the CNS, resulting in inflammation. Created with BioRender.com

production of proinflammatory cytokines. Subsequently, different subsets of CD4 + T cells will be activated against ZIKV, leading to its neuropathogenesis [32]. In addition to the production of inflammatory cytokines, higher levels of chemoattractive molecules produced by the ZIKV-infected blood–brain barrier (BBB) cells such as CCL5, CCL2, and CXCL10 increase the influx of immune cells into the CNS, which eventually leads to an inflammatory reaction in the CNS [33, 34]. Besides, ZIKV-induced CCL5 production could inversely affect the myelination process. Last but not least, ZIKV can affect other cells in the nervous system except for neurons. Some studies have shown that ZIKV induced morphological changes in astrocytes and fibroblasts, which might contribute to the neuropathogenesis of ZIKV [32].

Varicella-zoster virus

Varicella-zoster virus (VZV), known to cause chickenpox infection in humans, is one of the most frequent viral infections, affecting about 95% of adults in developed countries. After the initial infection, it establishes latency in the dorsal ganglia of most healthy people, which then might reactivate in particular circumstances [35]. Some studies have confirmed a positive association between VZV infection and the risk of developing autoimmune diseases such as MS [36–38]. A survey of a large population of MS patients and healthy individuals demonstrated that antibodies against VZV and CMV were significantly higher in MS patients than in healthy individuals [39]. Furthermore, unlike healthy individuals, the presence of VZV particles has been established in the urine of MS patients [40]. Likewise, CNS examination of MS patients has shown a higher percentage of VZV particles in the MS patients' CNS than in healthy individuals [41]. Interestingly, several studies have revealed that the VZV viral load in the CNS and peripheral blood of MS patients in the relapse phase was significantly higher relative to the remission phase [42], highlighting the hypothesis that VZV might play a role in developing or exacerbating MS symptoms. However, others have failed to show the presence of VZV virions or DNA in the CSF in the acute plaques of MS patients, which calls into question the validity of this hypothesis.

Molecular mimicry, as an old hypothesis for explaining the possible role of viruses in inducing autoimmune diseases also has been suggested for the relationship between VZV and MS development. Degrees of molecular mimicry exist between VZV glycoprotein E and Heterogeneous Nuclear Ribonucleoprotein A1 (HNRNPA1), which is present in the nucleoplasm as it shares > 62% amino acid sequence similarity with the prion-like domain (PrLD) of HNRNPA1, signifying the reason behind autoantibodies against M9 and PrLD of HNRNPA1. HNRNPA1 mutation might stimulate the presence and enhancement of HNRNPA1 in the cytoplasm, along with the presentation of the protein by MHC-1, which all trigger a cascade of immune reactivation [43].

Bearing in mind all considerations, the evidence favors the contributing role of VZV in inducing MS. However, further studies with more rigorous methodologies are needed to support this hypothesis.

Epstein–Barr virus

Epstein–Barr virus (EBV) is a ubiquitous member of the gamma-herpesvirus subfamily that is common in humans. The silent infection and the life-long persistence are the keys to the widespread infection of EBV in the human population. The virus is a linear DNA virus that encodes about 100 proteins and 44 micro RNAs (miRNAs). While many EBV miRNAs have no known function, there is evidence suggesting the role of viral miRNAs in innate immunity by regulating the inflammasome component NLRP3, the natural killer group 2D (NKG2D) ligand MICB, and the chemokine CXCL11 [44–46].

Following initial infection, EBV crosses the Waldeyer's ring to infect the naïve B cells. The activation of these naïve B cells to proliferating lymphoblasts is mediated via the Epstein-Barr nuclear antigen (EBNA). The activated lymphoblasts then migrate to germinal centers where they undergo a germinal center reaction to access their primary target (resting memory B cells) for latent persistence. The signals from the EBV encoded latent membrane proteins (LMPs) contribute to the survival of these infected lymphoblasts. It is noteworthy that given the type of latency, the virus expresses different sets of latent products including LMP1 and LMP2 [39, 40].

It is believed that EBV-associated pathologies result from the disruption of the virus-host immune system balance, and clinical manifestations of EBV infection emerge as a result of provoked immune response rather than EBV itself. In this regard, several studies have shown the immune response to EBV is disturbed in MS patients. *Sumaya* et al. were the first ones who described an increased frequency of antibodies to EBV in patients with MS compared to healthy controls. Since then, many studies have demonstrated increased antibodies against EBV antigens titer in MS patients [47–49]. Moreover, several studies have revealed evidence of EBV particles or EBV genomes in the brain tissue samples of MS patients [50]. Interestingly, in a recent issue of Science, *Bjornevik and Cortese* et al. utilized longitudinal evaluation of over 10 million adults between 1993 and 2013 to demonstrate the association between EBV infection and MS development. They showed a 32-fold increase in the risk of MS following EBV infection, but the risk was not increased after other viral infections. Moreover, neurofilament light chain levels were increased only after EBV seroconversion.

Notably, many hypotheses have been proposed to express the role of EBV in developing MS. Molecular mimicry has repeatedly been suggested as a potential pathogenic mechanism. The LMP1 mimics CD40 receptors, which play a role in B and T-cells interactions, and LMP2A mimics B-cell receptors. Moreover, an IL-10-like cytokine that EBV produces is crucial to B-cell activations [51]. In addition, patients with MS exhibit a more robust humoral response to EBNA-1, EBNA411–426, and EBNA1400–413, which can interact with some peptides of the myelin essential proteins as glial cell adhesion molecule (GlialCAM) [52, 53]. Likewise, elevated antibodies against the chloride-channel protein anoctamin 2 are seen in MS patients, which could cross-react with one of the EBNA1 peptides [54]. The molecular mimicry between EBV antigens and MS autoantigens has been confirmed in animal models. Namely, stimulation of mice with EBNA411–426 has been shown to increase the portion of T cells (IFN-γ producers) in response to MBP, leading to EAE [53].

Furthermore, it seems there is a relationship between EBV-infected B cells and the development of MS. Notably, EBV micro RNAs can protect EBV-infected B cells from CD8 + T cell response by reducing the EBV-specific CD8 + T cell proliferation and IFN-γ secretion [46]. Interestingly, it has been demonstrated that the number of T cells that recognize EBV-infected B cells decreases in MS subjects [55]. In addition, in contrast to healthy individuals, the latent-specific CD8 + T cells population is significantly greater than the lytic-specific CD8 + T cells [55, 56]. Moreover, IFN-γ secreted by CD8 + T cells hampers the EBV-infected B cell's proliferation and decreases the function and number of EBV-specific CD8 + T-cells, which results in intact EBV-infected B cells [57]. Therefore, it can be concluded that in healthy people, EBV-specific CD8 + T cells with an appropriate ratio of the lytic and latent specific CD8 + T cells could kill the EBV-infected cells. However, the number of lytic-specific CD8 + T cells is insufficient in MS patients, limiting their ability to regulate the EBV infection effectively.

Moreover, while the number of EBV-latent CD8 + T cells is significantly higher in MS patients, it is insufficient to prevent the growth of infected memory B cells. What is more, after a while, they show exhaustion which leads to more inefficiency [55].

Interestingly, regarding the role of EBV in the development of MS, particular attention has been paid to treatment strategies in this field. For the first time in 2014, *Pender* et al. applied the vitro-expanded autologous EBV-specific CD8 (+) T cells directed against viral latent proteins to treat a patient with secondary progressive MS. Their results were promising with no adverse effects and evidence of clinical and MRI improvement. Since then, many efforts have been made in this regard. More ever, there is a possibility that currently available B cell depleting therapies might be regarded as anti-EBV therapies, which deplete circulating memory B cells, the primary site of latent EBV infection [58]. The mechanism of Epstein-Barr Virus-induced CNS damage is given in Fig. 2.

HTLV-1

The human T-lymphotropic virus type 1 (HTLV1) is a single-stranded RNA virus that belongs to the *Retroviridae* family, the *Orthoretrovirinae* subfamily, and the deltaretrovirus genus, preferentiallyinfects $CD4^+$ T cells in vivo [59]. The HTLV1 genome contains diversified structural genes such as Pol, Gag, and Env, encoding the proteins of enzyme and viral structure, regulating genes including Tax, Rex, and accessory genes including p12, p21, p30, p13, and HTLV-1 basic leucine zipper factor (HBZ). HTLV-1 possesses different strategies to evade host immune responses. Among viral genes, Tax and HBZ play an essential function in the pathogenesis of HTLV1-induced diseases.

HTLV1 affects approximately 5–10 million persons worldwide. Most infected individuals remain asymptomatic; however, a portion of HTLV-1-positive individuals will develop HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), adult T-cell leukemia/lymphoma (ATLL) disease, and HTLV-1-Associated

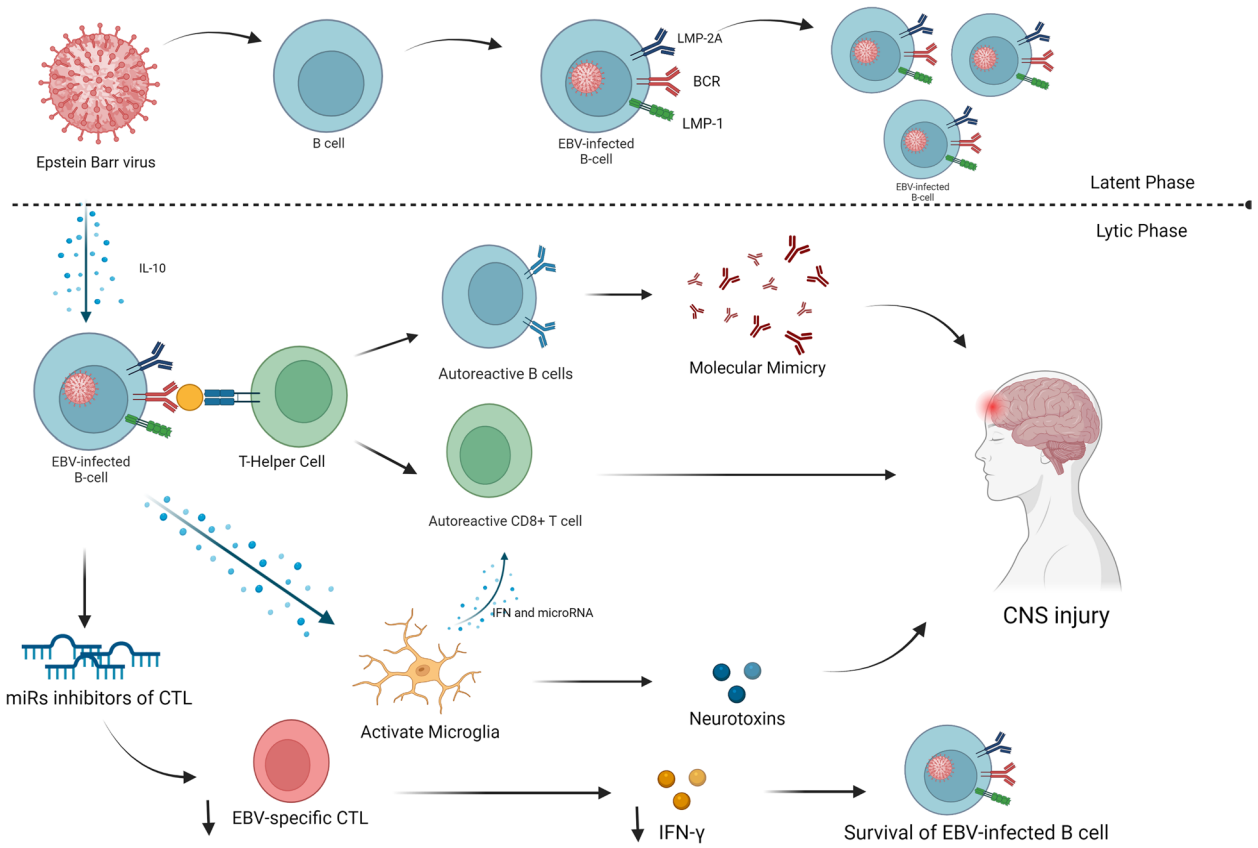

Fig. 2 The mechanism of Epstein-Barr Virus-induced Nervous System damage. EBV life cycle has two phases, including latent phase which provided proliferated viruses without immune reactions. When the number of viruses increased, the immune system reacted against viruses. The EBV-infected B-cells activate which subsequently activate adaptive lymphocytes. The EBV-infected B-cells produce some microRNAs that decrease EBV-specific T-cells and IFN-γ production which resulted in sustained EBV-infected B-cells. Prolonged EBV infections cause changes in the neuroprotective state of microglia to the neurodegenerative state which include neurotoxin production and activation of immune cells. Created with BioRender.com

Uveitis [60]. HAM / TSP is a progressive chronic inflammatory disease of the CNS, which mainly manifests with slowly progressive spastic paraparesis and significant sphincter impairment. Given the similarities with some forms of MS, HAM / TSP might be misdiagnosed with MS. Interestingly, there are few reports on the co-occurrence of MS and HTLV1 [61, 62].

In HAM/TSP patients, the Tax mRNA level is significantly higher than in healthy people [63]. The Tax protein directs ATF/CREB pathway and expresses viral genes [64]. Moreover, Tax through NF-κB activation induces cellular gene transcription and alters HTLV-1-infected cells [64]. It also stimulates T cell activation and proliferation in HAM / TSP patients by increasing the expression of IL-2 genes, IL-2 receptor domain an (IL-2Ra), IL-15, and IL-15Ra [65–69]. Tax-induced elevations in IL-2, IL-9, and IL-15 activate the Jak3/STAT5 axis, and Jak3 blockade has been found to reduce the immunological stimulation in PBMCs in HAM/TSP patients [70]. HBZ inhibits the NF-B pathway and decreases Tax activity via interacting with the CREB/ATF pathway [71]. Numerous studies have shown that in HAM / TSP patients, the activity of Treg cells and the expression of Foxp3 are significantly reduced, which is assumed to be the result of Tax overexpression [72–75]. In addition, recent studies have demonstrated that the Tax protein could inhibit the TGF-β gene expression through disruption of TGF-β signaling expression [76]. Decreased numbers of CD4 + CD25 + Foxp3 + Treg cells were seen in transgenic rodents expressing HTLV-1 Tax that expands an inflammatory arthropathy [77]. It has been revealed that the $CD4^{+}CCR4^{+}$ T cells that coexpressed the Th1 marker CXCR3 and produced T-bet and IFN-γ were present in the CSF and spinal cord lesions of HAM/TSP patients [78]. Being activated by IFN-γ, astrocytes release CXCL10, attracting additional CXCR3 + T-cells to the CNS. This situation creates an inflammatory positive feedback loop, accompanied by subsequent fabric damage [79].

HSV-1

Herpes simplex virus type 1 (HSV-1) is a part of the *herpes simplex* family with a double-stranded DNA-encapsulated virus [80]. HSV-1 is a ubiquitous virus affecting more than 60% of people worldwide. However, only 20 to 40% of infected people show clinical symptoms varying from mild skin involvement to severe peripheral and central nervous system infection [81]. The HSV-1 has two infectious phases, which include the lytic and latent phases. In the latent phase, the infectious virus is produced, while the viral components are not detectable in the individual [82]. During the HSV-1 lytic phase, it expresses an orchestrated of viral genes in the virus-infected cells, including three main categories of gene expression: immediate early gene, early gene, and late gene [83]. On the other hand, HSV-1 encodes several factors to escape the immune system, which causes the virus to persist for a long time. Notably, while during latency there is limited gene expression and no production of viral particles, the viral genome still has potential for reactivation, leading to the production of infectious virions upon the appropriate stimulus [84].

The mechanisms leading to latency and reactivation and which are the viral and host factors controlling these processes are not completely understood. The Us6 gene encodes glycoprotein D, which is a part of HSV construction is required for penetrating the host cells, and inhibiting the apoptosis by activating NF-κB and enhancing NF-κB-dependent anti-apoptotic genes such as FLIP and c-IAP2 [85, 86]. Glycoprotein E has been shown to act as an inhibitor of apoptosis in epithelial cells and is produced by activating ERK1/2, which is associated with the degradation of the Bim protein [87]. ICP22 is another HSV-1 protein that plays a negative role in apoptosis [88]; the deleted ICP22 recombinant HSV-1 induces more apoptosis compere to unmanipolated virus [89]. Another mechanism is disruption of the autophagy process, a process that removes the damaged organs and prevents the accumulation of misfolded proteins, leading to the cellular hemostasis [90]. Animal studies have shown that Atg5 and Atg7 are essential proteins for autophagy; therefore, mice with defects in the Atg5 [91] and Atg7 [92] proteins have provided evidence of neurodegenerative diseases In this regard, HSV1 inhibits the cellular protein synthesis, impeding the virus replication through eukaryotic initiation factor 2a (eIF2a) phosphorylation, which is known to be involved in controlling HSV-1 in neurons [93].

In terms of neurotoxicity, herpes simplex encephalitis (HSE) is considered as the most devastating manifestation of HSV-1. It can occur either in primary infection or upon reactivation from latency. Cytolytic HSV-1 proliferation and immune factors are involved in the development of HSE [94–97]. The intrinsic and innate immune responses are key to protect against HSV-1 infection of the CNS and subsequent pathologies, including HSE. Toll like Receptors (TLRs) are parts of the innate immune system that provide the first line of defense against viral infection. HSV-1 infection in astrocytes activates TLR2 and TLR4, which causes IFN-I expression and an increase in pro-inflammatory cytokines such as IL-6 [98]. TLR3 also plays an important role in controlling HSV-1 infection. It detects viral double-stranded RNA which is produced during HSV-1 replication, inducing the production of type I IFNs [99]. HSV-1 neuro-infection induces the expression of cytokines and pro-inflammatory molecules such as TNF-a, IL-6, IL-8, CCL5, CXCL10, and

macrophage inflammatory protein 1a (MIP-1a) in the brain [100, 101]. During the acute phase of HSE, macrophage and neutrophile cells enter the brain, triggering an immune response to eliminate the infection [102, 103]. Penetrated macrophages secrete TNF-α, and microglial cells express IL-1B [104]. Moreover, infiltrating CTL cells detect the HSV-1 glycoprotein B and promote the neural infected cells' death [105]. T lymphocytes are the primary leukocytes in the brain 14 days after infection, and CD8 + T cells express IFN-γ, which cooperates with TNF-α and increases NO-induced neurodegeneration and demyelination [106]. Ideally, the immune response controls the virus. Otherwise, an uncontrolled and excessive immune response might be detrimental.

Interestingly, there is evidence suggesting the potential link between HSV and Alzheimer's disease (AD). HSV-1 DNA has been shown to be co-located with amyloid B in the brain tissue samples of patients with AD. The association between HSV-1 and AD is stronger in individuals carrying the APOE4 allele, one of the strongest genetic risk factors for AD [107]. Moreover, HSV-1 causes the accumulation of AB1-40 and AB1-42 and reduces ABPP levels, hallmarks of AD pathology, which indicates a predisposing factor in AD [108]. There is also evidence of mitochondrial pathway disruption in virus neurotoxicity. Several studies have shown that HSV-1 infection increases the Reactive Oxygen Species (ROS) levels, which have been demonstrated to play a role in development of AD [61, 109]. TLR2.

Regarding the association of HSV1 and MS, the scope of article is inflammatory disorders.

Influenza

Influenza virus is an enveloped, negative-sense single-stranded RNA virus that consists of 8 parts and is classified as the *orthomyxoviridae* family membership [62]. Influenza virus known as three different subtypes, including A, B, and C, whereas influenza A and B are the primary pathogens in humans [110]. Currently, 18 hemagglutinin (HA) subtypes and 11 neuraminidase (NA) subtypes were investigated [111]. HA binds the virus to the sialic acid receptor, which causes the membrane to fuse and enter the cell. NA is a receptor-degrading enzyme that is required for virus release and virus spread [112]. Infections alone cannot induce autoimmune diseases and other factors such as genetics, hormones, and immunity are also involved [113]. However, there is evidence that the infections play a role to induce autoimmune diseases such as Guillain-Barré syndrome, Multiple Sclerosis, and Autism [94]. Influenza has been identified as a trigger for MS. One study found a positive association between the occurrence of influenza and MS [95]. A case–control study also showed that IgG against several viruses, including Influenza A, was higher in MS patients than in controls [96]. However, another study has shown that the Influenza vaccine does not affect the risk of developing MS [97]. Among the reported autoimmune complications, GBS is the most commonly reported autoimmune disease caused by the Influenza vaccine [114]. Sivadan Tardy et al. in France demonstrated that there was a positive correlation between the monthly prevalence of GBS for unknown reasons and the number of Influenza patients. Although influenza serology has low accuracy in diagnosing influenza, there has been a significant association between GBS patients and influenza A and B [115]. In another study in the UK, Tam et al. examined the risk of developing GBS after catching influenza and found that the risk of developing GBS increased within two months of catching the Influenza [116].

The influenza virus genome is detected by TLR7, while during virus replication, double-stranded RNA is detected by TLR3. Activation of the corresponding TLRs by ssRNA or dsRNA activates the signal cascade. TLRs are not required to activate T cells against influenza. However, they induce B cell responses directly and indirectly by INF-α [117], which stimulate B cells to proliferate, switch to the IgG antibody class, and produce autoantibodies. Influenza-infected cells also produce IFN-α, which causes DC to mature and activate T cells. One possible response to autoimmune diseases following influenza infection is to reduce the down-regulation of DC cells, which increases the number of activated cells [118]. Influenza virus can also stimulate pro-inflammatory cytokines such as IL-8, which can cause autoimmune diseases [119]. Another response to autoimmune diseases is "molecular mimicry," which is antigen-dependent, and the immune system responds to similar antigens to microbial segments [120]. GBS is a peripheral nervous system (PNS) autoimmune disease, usually established following infection. GBS, Fisher syndrome (FS), and Bickerstaff brainstem encephalitis (BBE) are considered as GBS-related disease (GBSRD). Anti-glycolipid antibodies are raised in GBSRD and involved in the pathogenesis. The anti-GM1 antibody is found in GBS after infection with C.Jejuni, and the antibody against galactoserbroside is found in neurological diseases after infection with M.Pneumonia [121, 122]. The carbohydrate component of neurons is similar to carbohydrates produced by infectious agents, recommending molecular mimicry is responsible for GBSRD [123, 124]. Although anti-glycolipid antibodies are more abundant in C.Jejuni-induced GBS (GBSRD-C) than influenza-induced GBS and anti-GM1 antibodies are more abundant in Influenza-induced GBSs, anti-GQ1b is significantly higher in influenza-induced GBSRDs [125]. Moreover, Anti-GT1a is also

moderately more common in Influenza -induced GBSRD patients [125]. Nachamkin et al. [126] studied the role of the A / NJ / 1976 influenza vaccine in causing an inappropriate immune response in mice. All vaccines against mice were able to induce the production of antibodies against HA, especially GM1. Studies showed that vaccine A / NJ / 1976 and subsequent vaccines had a Glycan layer that antibodies could immunohistochemically stain against GM1. Moreover, viral HA, which usually binds to sialic acid, can form the sialic acid-HA complex, which is destroyed by NA. Low NA levels because incomplete removal of sialic acid from viral HA can eventually mimic the structure of GM1 [126, 127].

SARS-CoV2

SARS-CoV2 is an enveloped, positive-sense, single-stranded RNA (ssRNA) of the *coronaviridae* family [128–130]. Coronaviruses are classified into four genera: Alphacoronavirus (αCoV), Beta coronavirus (βCoV), Gamma coronavirus (ϒCoV), and Delta coronavirus (δCoV). Human coronaviruses (HCoV) belong to α- and βCoVs [131, 132] and a newly emerged HCoV, SARS-CoV2, was clustered with lineage βCoV [133, 134]. Studies in Covid-19 patients have shown that after the outbreak of SARS-CoV-2, reports of neurological complications such as GBS [135], AD [136], Parkinson disease(PD) [136], and MS have increased [103]. So far, the neurologic manifestations related to SARS-CoV-2 infection were reported widely varied. The pandemic results from COVID-19 revealed that the association between the incidence of Guillain–Barré syndrome (GBS) and previous SARS-CoV-2 infection is not very clear [137]. It was reported that GBS numerate as one of the frequently manifested PNS complications for COVID-19 [138]. The first case of GBS has been reported in a 61-year-old COVID-19-positive woman [131]. Recently, numerous case reports have been reported around the world in COVID-19 patients [139, 140]. Possible association between SARS-CoV-2 vaccination and GBS have been reported in several researches [98, 141]. In various epidemiological studies the association between GBS and SARS-CoV-2 infection have been investigated, as some of these studies finds no association between COVID-19 and GBS [142]. However, in some studies contradictory data have been reported. Palaiodimou L and et al. reported that among 136,746 COVID-19 patients the pooled GBSs prevalence was estimated 15 cases per 100,000. Also, they found that COVID-19 patients had increased odds for demyelinating GBSs subtypes [143]. In one retrospectively study, Restrepo-Vera JL and et al. investigated the relationship between GBS and SARS-CoV-2 infection, as findings showed a clear increase in GBS cases at the expense of a significant number of GBS-S. It was reported that this contradictory findings may be explained by a decrease in the number of cases of GBS associated with other infections due to the wearing mask, hand hygiene, and social distancing [99, 144, 145]. In a retrospective cohort study, Wang L and et al. investigated whether SARS-CoV-2 viral infection is associated with increased risk for AD. Of the 6,245,282 older adults (age ≥ 65 years) enrolled in the study, they found that people with COVID-19 were at significantly increased risk for new diagnosis of AD within 360 days after the initial COVID-19 diagnosis, especially in people age ≥ 85 years and in women [146]. Li S and et al. investigated ecological time-series analysis of AD and PD mortality during the COVID-19 pandemic in the USA. Findings revealed that from March 2020 to March 2022, the number of 41,115 and 10,328 excess deaths have been reported for AD and PD, respectively. This excess mortalities for AD and PD were about 23 and 9 times higher than those aged 55–84 years, respectively. Also, it was reported that females had a three-time higher excess mortality of AD than males [100]. In a retrospective cross-sectional study, Gilstrap L and et al. investigated the association between mortality among older adults with Alzheimer disease and related dementias (ADRD). Findings revealed that compared with 2019, adjusted mortality in 2020 was 12.4% higher among enrollees without ADRD and 25.7% higher among all enrollees with ADRD among 53 640 888 Medicare with 65 years of age or older [101]. Related to the MS, we did not find any retrospective cohort study with large size to validate the association between the increase of the MS at the age of COVID-19 disease. Most of the studies focused on the prevalence of COVID-19 infection in patients with multiple sclerosis (MS), and did not clearly investigate the increase of the MS at the age of COVID-19 disease. Some data support that the hospitalization rate is higher among MS patients based on COVID-19 infection [102]. It was reported that CNS demyelination has occurred shortly after COVID-19, suggesting that these symptoms could be the result of neurological damage following SARS-CoV-2 infection, or they could be coincidental, from causes such as secondary systemic complications or side effects of drug treatment [102, 103].

SARS-CoV-2 requires the angiotensin-converting enzyme 2 (ACE2) as a functional receptor to penetrate cells. The virus binds to the ACE2 receptor via the spike, although the virus has also been observed to use Basigin (CD147) and Neuropilin-1 (NRP1) as receptors [104]. After SARS-Cov-2 infecting the cells, PRRs identified PAMP and DAMP of viruses and induced inflammatory reaction [18]. Following SARS-COv-2 entrance, infected neural cell can kill directly or indirectly though using immune system. Moreover, neurodegenerative process was conducted as an acute and chronic phase. Indirect

damage proceeded in several mechanisms, including molecular mimicry, cytokine storm which induce self-antigens productions, and autoantibodies production.

Molecular mimicry is the one of the main proposed mechanism involved in neurodegeneration which can cause the immune system to become overactive in autoimmune diseases are similar to those of the immune response against SARS-CoV2 [105]. Molecular mimicry involves the structural similarity of SARS-CoV2 antigens to their self-antigens, which activate the B cells and T cells against human-like proteins, which causes autoimmune diseases [105]. Molecular mimicry is the most common cause considered for GBS. Anti-ganglioside antibodies were identified in the 50 to 85 percent of GBS patients. The rise in anti-ganglioside antibodies in GBS patients with Covid-19 remains unclear; however, Dufour, et al. found the presence of anti-GM1 antibodies in GBS patients infected with Covid-19 [106]. Furthermore, among 58 Covid-19 patients with neurological symptoms, SARS-CoV-2 was identified in the CSF of only two patients [147] the inability to identify SARS-CoV-2 genome in the CSF of most patients indicates that direct virus attack does not involved in the autoimmunity [104]. Another mechanism for autoimmune diseases in Covid-19 patients is the aberrant immune system's response to SARS-CoV2, which triggers the inflammatory cytokines and chemokines production, including IL-1B, IL-6, IL-8, TNF-a, IFN-γ, Granulocyte colony-stimulating factor (G-CSF), induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein 1a (MIP-1a) [18]. This aberrant immune reaction to the virus triggers the cytokine storm and production of inflammatory conditions which induce disruption of self-tissue and produced SARS-Cov-2 antigens-mimicking which is involved in the pathogenesis neurodegenerative disorders [148]. The pathogenesis of MS is not fully understood; however, several studies demonstrated that immune response and inflammation lead to MS. Studies have shown that inflammatory cytokines such as IL-12, IL-17, IFN-γ, and TNF-a are significantly higher in the CSF of MS patients [149]. In Covid-19 patients, Th17 levels increase, which regulates inflammatory conditions by increasing IL-6 and IL-23, indicating the pivotal role of this cell in the production of Cytokines Storm, which provides the requirements for MS [150]. Following the production of these self-antigens due to the cytokine storm, antigen presenting cells promote the T cells and induced autoreactive responses which results in further undertaken neurodegeneration. Moreover, upon self-tissue damaged, de novo new self-epitopes are produced which further induce autoreactive T cell activation and sustained neurodegenerative process. Additionally, memory process of immune system encourages production of further antibodies versus different nervous system tissue, such as blood–brain barrier and myelin sheet which results in prolonged and severe neurodegenerative process in the overed-Covid-19 state [151] (Fig. 3).

Following the emergence of covid-19, vaccination against SARS-Cov-2 is considered as an effective strategy for preventing infected to covid-19 and decreasing the severity and mortality of patients infected by SARS-Cov-2. However, some clinical studies reported the patients with novel neurological autoimmune diseases who is diagnosed after receiving covid-19 vaccines. Rinaldi et al. reported the patients with CNS inflammatory demyelinating events following covid-19 vaccine administration. They showed that covid-19 vaccine can induce acute transverse myelitis, MS, acute demyelinating encephalomyelitis (ADEM), and neuromyelitis optica spectrum disorder (NMOSD) [152]. Moreover, Abdelhady et al. reported 65 patients who developed encephalitis following covid-19 vaccines [153]. Despite first presentation of MS after covid-19 vaccine was reported in some studies [154–157], Stefanou et al. showed that Covid-19 vaccination is not associated with increasing the risk of relapse of patients with MS irrespective to the type of covid-19 vaccines [158], and therefore, most of the patients with MS are willing to receive covie-19 vaccine [159].

Conclusion

Autoimmune diseases are frequently developed based on the interaction between several factors, including genetic susceptibility, aberrant immune response, and environmental factors such as infections. The viral infection seems more critical to inducing autoimmune disease disorders. The exact level of involvement of these factors was not elucidated [160]; however, several studies revealed that viruses could caus [161] or exacerbate [162, 163] autoimmune disease. In contrast, accumulating data suggest that viruses regulate the immune response and protect against the onset of autoimmune diseases [3]. Viruses can induce several immune pathways, resulting in an aberrant immune response. The mechanisms, including bystander activation, cryptic antigens presentation, epitope spreading, and molecular mimicry, were considered the main pathways to induce autoimmune reactions in general autoimmune diseases [160]. Based on the complex nature of the nervous system, it is expected that viruses cause autoimmune diseases of the nervous system in more complex ways. In this review, we summarized the investigated mechanisms of viruses-induced neurological autoimmunity. We showed that viruses promote different gene expressions and cause immune system over-activation and cytokine storms alongside previously known

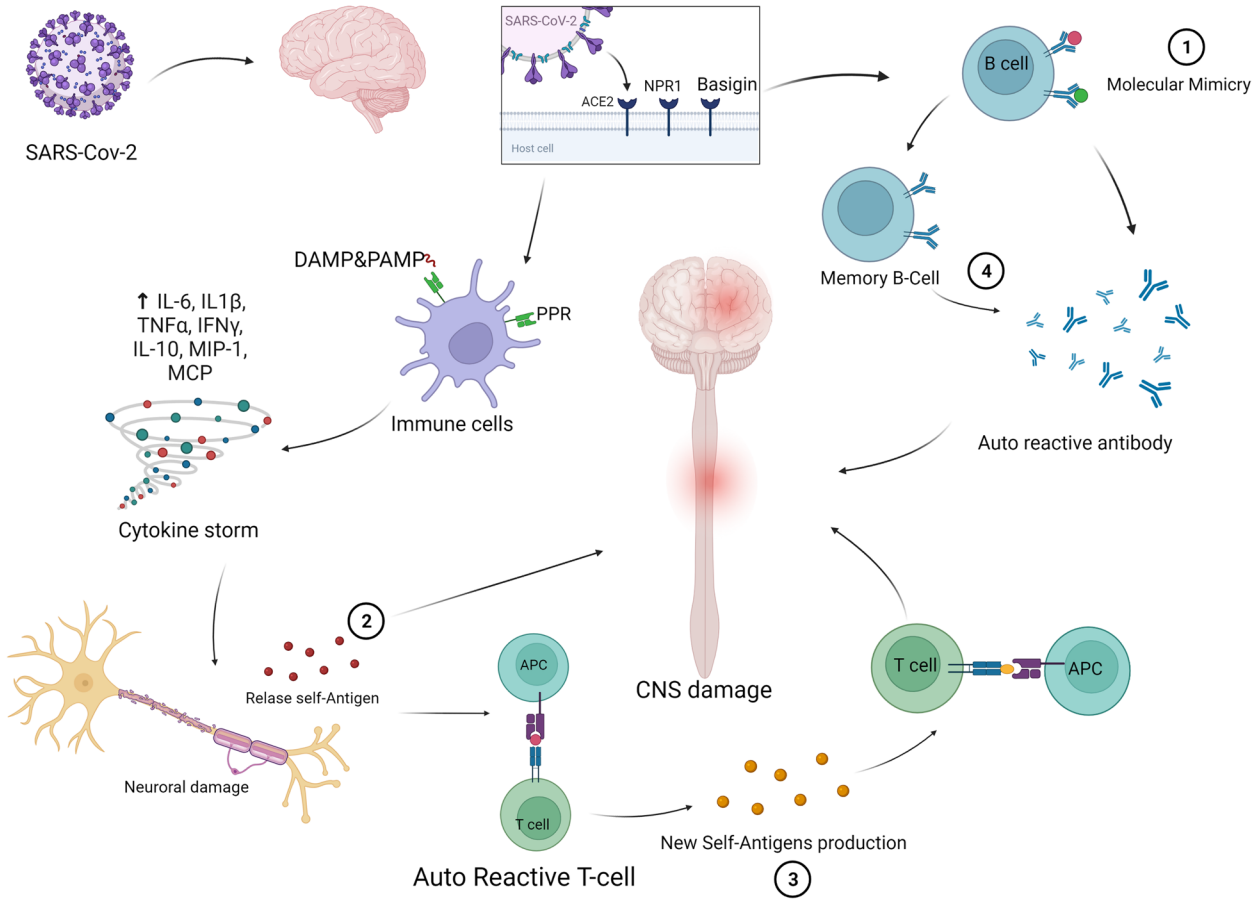

Fig. 3 The mechanism SARS-Cov-2 induces neurological autoimmune system. SARS-Cov-2 enters the nervous system through different receptors. The viruses induce autoimmune reactions through several pathways. 1) The B- cells produce autoreactive antibodies against SARS-Cov-2, which damaged the normal tissues. 2) The recognized virus through PRR induces cytokine storm, resulting in damage to the healthy tissue and new antigens that, releases activate autoreactive T-cells. 3) Subsequently, the T-cell reaction destroys tissues and produce new self-antigens, which induce more autoreactive T-cells reaction. 4) The memory B-cells produce long-term autoantibodies in the absence of virus, which was associated with sustained CNS damage—created with BioRender.com

mechanisms of general autoimmune disease induced by viruses, resulting in immune-mediated tissue injury. Conclusively interactions of Host (Genetic and Immune system) and viral factors can determine how the immune system induces effective or pathologic response.

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Authors' contributions
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Availability of data and materials
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Declarations

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