



Understanding the link between neurotropic viruses, BBB permeability, and MS pathogenesis

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Abstract

Neurotropic viruses can infiltrate the CNS by crossing the blood–brain barrier (BBB) through various mechanisms including paracellular, transcellular, and “Trojan horse” mechanisms during leukocyte diapedesis. These viruses belong to several families, including retroviruses; human immunodeficiency virus type 1 (HIV-1), flaviviruses; Japanese encephalitis (JEV); and herpesviruses; herpes simplex virus type 1 (HSV-1), Epstein-Barr virus (EBV), and mouse adenovirus 1 (MAV-1). For entering the brain, viral proteins act upon the tight junctions (TJs) between the brain microvascular endothelial cells (BMECs). For instance, HIV-1 proteins, such as glycoprotein 120, Nef, Vpr, and Tat, disrupt the BBB and generate a neurotoxic effect. Recombinant-Tat triggers amendments in the BBB by decreasing expression of the TJ proteins such as claudin-1, claudin-5, and zona occludens-1 (ZO-1). Thus, the breaching of BBB has been reported in myriad of neurological diseases including multiple sclerosis (MS). Neurotropic viruses also exhibit molecular mimicry with several myelin sheath proteins, i.e., antibodies against EBV nuclear antigen 1 (EBNA1) aa411–426 cross-react with MBP and EBNA1 aa385–420 was found to be associated with MS risk haplotype HLA-DRB1*150. Notably, myelin protein epitopes (PLP₁₃₉₋₁₅₁, MOG₃₅₋₅₅, and MBP₈₇₋₉₉) are being used to generate model systems for MS such as experimental autoimmune encephalomyelitis (EAE) to understand the disease mechanism and therapeutics. Viruses like Theiler’s murine encephalomyelitis virus (TMEV) are also commonly used to generate EAE. Altogether, this review provide insights into the viruses’ association with BBB leakiness and MS along with possible mechanistic details which could potentially use for therapeutics.

Keywords Multiple sclerosis · Blood–brain barrier · Neurotropic virus · EAE

Abbreviations

AIDS	Acquired immunodeficiency syndrome	HAD	HIV-1-associated dementia
BBB	Blood-brain barrier	HAD	HIV-1-associated dementia
BMECs	Brain microvascular endothelial cells	HERVs	Human endogenous retroviruses
CMV	Cytomegalovirus	HHV-6	Human herpesvirus 6
EBNA1	EBV nuclear antigen 1	HIV-1	Human immunodeficiency virus type 1
EBV	Epstein-Barr virus	HPV	Human papillomavirus
EAE	Experimental autoimmune encephalomyelitis	HTLV-1	Human T-cell leukemia virus
ERK1/2	Extracellular signal-regulated kinase 1/2	IL-1β	Interleukin-1 beta
CalHV3	Gamma-herpesvirus callitrichine herpesvirus 3	JEV	Japanese encephalitis
HCV	Hepatitis C virus	JCV	John Cunningham virus
HSV-1	Herpes simplex virus type 1	JAM	Junctional adhesion molecules
		LCMV	Lymphocytic choriomeningitis virus
		MMPs	Matrix metalloproteinases
		MNC	Mononuclear cell
		MAV-1	Mouse adenovirus 1
		MS	Multiple sclerosis
		MBP	Myelin basic protein
		MOG	Myelin oligodendrocyte glycoprotein
		MAG	Myelin-associated glycoprotein
		NVU	Neurovascular unit

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PT	Pertussis toxin
PLP	Proteolipid protein
TMEV	Theiler's murine encephalomyelitis virus
TJs	Tight junctions
TTV	Torque-teno virus
TNF- α	Tumor necrosis factor-alpha
VZV	Varicella-Zoster virus
VLPs	Virus-like particles
WNV	West Nile virus

Introduction

Numerous neurotropic viruses are commonly known to disrupt the blood–brain barrier (BBB) by triggering changes in the endothelial junctions through different entry mechanisms such as paracellular (between cells), transcellular (through cells), and “Trojan horse” (diapedesis of infected immune cells) (Chen and Li 2021; Spindler and Hsu 2012). These viruses include human T-cell leukemia virus (HTLV-1), human immunodeficiency virus-1 (HIV-1), West Nile

virus (WNV), lymphocytic choriomeningitis virus (LCMV), mouse adenovirus type 1 (MAV-1), herpes simplex virus (HSV), and Epstein-Barr virus (EBV). WNV and its virus-like particles (VLPs) may pass through brain endothelial cell (EC) transcellular without affecting the integrity of the BBB while the paracellular entry of viruses triggers alteration in the tight junction (TJ) proteins, basal lamina, and cytoskeleton (Delorme-Axford and Coyne 2011). The functionality of BBB is governed by an intricate interaction of cells like endothelial, pericyte, and perivascular astrocytes (Takeshita and Ransohoff 2012). Pericytes are present on the abluminal side of the endothelial layer, have long cytoplasmic processes which make contact with numerous ECs, and thus, integrate signals along the vessel's length and can also extend to more than one capillary (Bergers and Song 2005). During the disrupted BBB, the deposition of collagen, apoptotic changes in pericytes, and swelling of astrocytes have been observed (Fig. 1) (Claudio et al. 1995). Diminished BBB integrity showed continuous association with neurological diseases, namely, multiple sclerosis (MS), ischemic stroke, and traumatic brain injury (Profaci

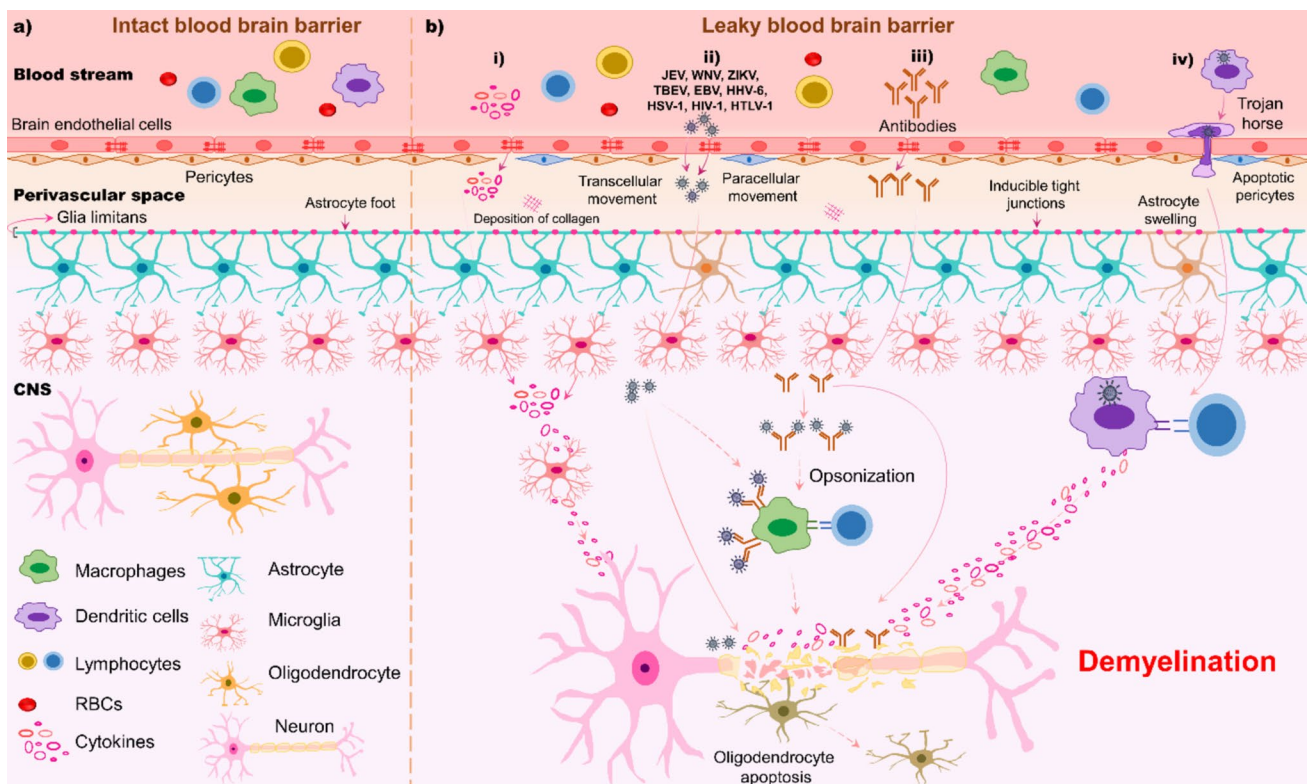


Fig. 1 **a** Illustration of a healthy condition with no viral exposure and inflammatory molecules. **b** Representation of debilitated BBB due to viral, inflammatory and immune autoreactive insults. **i** Viruses activate different immune cells and trigger release of cytokines, which eventually target brain endothelial cells and exudate into the CNS. **ii** Several RNA and DNA viruses directly breach BBB transcellularly/paracellularly and enter into CNS, reactivating brain cells such

as microglia and astrocytes. **iii** Autoantibodies primed against self-antigens (MBP, MOG, PLP, etc.) cross BBB follow the opsonization cascade and jeopardize the neuronal integrity by augmenting the cytokine storm. **iv** Several viruses follow the “Trojan horse” mechanism through diapedesis of immune cells. The disruption of BBB can be observed by the collagen deposition, pericyte apoptosis, and astrocyte swelling

et al. 2020; Höftberger and Lassmann 2017). MS, being an immune-induced disease of the brain, is characterized by disruption of myelin sheath in white matter, loss of oligodendrocytes, changes in the BBB integrity, and leucocyte infiltration (Höftberger and Lassmann 2017). The leaky BBB has been found in MS lesions and revealed as the key step in its pathogenesis and development of inflammatory regions around the venules (Kolb et al. 2022). The leucocyte transmigration across the vasculature and leaky BBB aid in neuroinflammation as observed in MS (Bradl and Lassmann 2010; Stamatovic et al. 2008).

Furthermore, the accumulation of perivascular fibrin provides an additional evidence for the chronic BBB anomaly in MS (Claudio et al. 1995). Several modulators like certain growth factors, cytokines/chemokines, matrix metalloproteinases (MMPs), various lipid mediators, and reactive oxygen species (ROS) affect this transcellular/paracellular BBB permeability of pathogens (Stamatovic et al. 2008). Likewise, chemokines also amend the binding affinity between the cell adhesion molecules (CAMs), triggering the infiltration of leukocytes and regenerative binding of T-cell with endothelium through intercellular adhesion molecule-1/lymphocyte function-associated antigen-1 (ICAM-1/LFA-1) and vascular cell adhesion molecule-1/alpha4beta1 integrin (VCAM-1/VLA-4) complexes (van Buul and Hordijk 2004). Then, the lymphocyte starts its migration process by adhering to the endothelial cell (Engelhardt and Wolburg 2004). Moreover, the increased permeability of BBB is also correlated with the clearance of therapeutic modalities against the neurotropic viruses in mice, suggesting an ineffective treatment against viral infections which eventually aid in MS (Fabis et al. 2007). The animal model commonly used for studying MS is experimental autoimmune encephalomyelitis (EAE), where autoimmunity is developed in the susceptible mice brain by administering the myelin and associated protein self-antigens (Robinson et al. 2014). Similarly, EAE can also be generated by using certain toxins like cuprizone and lysolecithin (Denic et al. 2011). Therefore, there are numerous studies available addressing these topics separately, and since these are overlapping topics, we aim to provide a summary of neurotropic virus-mediated BBB disruption and MS. Further, we have also mentioned the virus-associated mechanisms and highlight the significant viral as well as host protein molecules that can be a therapeutic target.

Viruses and unclashed blood–brain barrier

The BBB is held tightly by the TJs among the brain microvascular endothelial cells (BMECs). Pericytes and astrocytes cooperate with the BBB endothelium through several soluble factors along with neurons and form the neurovascular unit (NVU) (Sweeney et al. 2016). The disruption of BBB

is a hallmark of central nervous system (CNS) infections that can instigate by host immune factors [tumor necrosis factor-alpha (TNF- α) and interleukin-1 beta (IL-1 β)] or viral factors (Erickson et al. 2012). Viruses may cross the BBB via numerous routes, including direct infection into BMECs, entry of infected peripheral leukocytes, or trans/paracellular viral migration through the endothelium (Chen and Li 2021). Neurotropic viruses such as retroviruses, rhabdoviruses, flaviviruses, picornaviruses, morbillivirus, bunyaviruses, alphaviruses, herpesviruses, and coronaviruses are known to invade the CNS (Ludlow et al. 2016) (Fig. 1). Viruses invade into the CNS directly by crossing the BBB or bypassing the BBB through non-hematogenous routes (Miner and Diamond 2016). The direct virus transit across the BBB includes the following: (i) a prominent level of viremia and inflammation-stimulating viruses spread over BMEC TJs; (2) direct virus entry into BMECs and transport of newly developed virions through basolateral membranes; (3) infected leukocytes migrate through the BBB to seed infectious virus in CNS which is known as “Trojan horse” pathway (Miner and Diamond 2016). Some viruses utilize non-hematogenous routes to get access into CNS. These mechanisms comprise the following: (i) reverse axonal transport of virions from the peripheral nervous system (PNS) to CNS and (ii) olfactory epithelium challenged by viruses triggers their transit to the CNS through the cribriform plate and olfactory bulb (Ludlow et al. 2016). It is highly plausible that certain viruses may use more than one pathway to enter the CNS. For instance, the Venezuelan equine encephalitis virus invades the CNS by cribriform plate followed by the delayed BBB opening that allows the second time viral neuro invasion straight through the BBB (Schäfer et al. 2011).

Involvement of retroviruses in blood–brain barrier permeability

Human immunodeficiency virus type 1

Among neurotropic viruses, the human retroviruses HIV-1, HTLV-1, usually invade through the hematogenous route (Miller et al. 2012). HIV-1 triggers acquired immunodeficiency syndrome (AIDS) and, due to the inflammatory status of AIDS-infected cells, lacks the crosstalk between the immune and endothelial cells. Inflammatory cytokines are known to increase the permeability of BBB (Miller et al. 2012) (Fig. 1), although the degree of BBB disruption differs among neurotropic viruses. For example, HIV-1 majorly enters the CNS by a “Trojan horse” mechanism and induces mild disruption, while the HSV leads to a higher disruption that can raise CSF albumin levels, 50 mg/dl which is three to six times higher than the normal levels (Erickson et al. 2012). The HIV-infected monocytes circumvent the BBB during normal patrolling

of perivascular macrophages and eventually trigger the production of proinflammatory mediators, like chemokine ligand 2 (CCL2), which disrupt the BBB (Toborek et al. 2005). HIV-1 proteins, namely, trans-activator of transcription (Tat), glycoprotein 120 (gp120), negative factor (Nef), and HIV-1 viral protein R (Vpr), follow a mechanism of the cascade to disrupt the BBB and generate a neurotoxic effect (Maubert et al. 2017). Recombinant-Tat triggers downregulation in the expression of TJ proteins, e.g., zona occludens-2 (ZO-2), claudin-5, and claudin-1 in BBB cells (András et al. 2003). Likewise, the in-vivo challenge to recombinant-Tat triggered a redistribution of claudin-5 immunoreactivity (András et al. 2003). Besides, the Tat exposure in the brain hippocampus of mice (C57BL/6) resulted in the mitigation of ZO-1 mRNA levels and effectively reduced the ZO-1 continuity in brain microvessels (András et al. 2003). The above-stated changes are attributed to the induction of extracellular signal-regulated kinase 1/2 (ERK1/2), thus indicating that Tat-mediated oxidative stress is pivotally affecting BBB intactness via the ERK1/2 pathway (Pu et al. 2005). Moreover, Tat alters monocyte chemoattractant protein-1 (MCP-1) secretions from astrocyte/microglial cells and adhesion molecules in endothelial cells (Ajasin and Eugenin 2020). Intriguingly, an elevated risk of HIV-1-associated dementia (HAD) exhibited a correlation with the mutant MCP-1 allele (Ajasin and Eugenin 2020). In addition, BMECs express the HIV-1 co-receptors, i.e., C-X-C chemokine receptor type 4 (CXCR4) and C-C chemokine receptor type 5 (CCR5). Macrophage-derived gp120 (having CCR5 co-receptors) or lymphocytes (having CXCR4 co-receptors) were exposed to BMECs leading to reduce the BBB tightness and elevated monocyte migration across BBB (Kamogne et al. 2007). In contrast, the BBB integrity was refurbished after dispensing gp120 (Kamogne et al. 2007). According to an in-vitro study, antibodies against CCR5 and inhibitors for protein kinase C (PKC) and myosin light chain kinase blocked gp120-mediated surge of monocyte migration and eventually BBB permeability (Louboutin and Strayer 2012). Gp120 triggers the activation of three different isoforms of PKC in BMECs (PKC (pan)-bII, PKC-f/k, and PKC-a/bII). Besides, inhibitors against PKC targeting the ATP-binding and calcium release site block gp120-induced PKC activation and eventually increase the permeability of BBB (Kamogne et al. 2007). Further, an in-vivo investigation also demonstrated the invasion of HIV-1 envelope protein into the murine brain (Banks et al. 2001). Depletion of capillary has shown that the radioactively labelled envelope glycoprotein⁺ (Env⁺) virus completely passes through the endothelial barrier of the brain to enter the CNS parenchyma while enveloping glycoprotein⁻ (Env⁻) moiety has not shown any BBB crossing (Banks et al. 2001).

Human T-cell leukemia virus 1

HTLV-1 is also associated with numerous long-term neurological disorders called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HAM/TSP triggers BBB amendments such as the deposition of fibrinogen and immunoglobulin in the CNS parenchyma and the maneuver of lymphocytes carrying HTLV-1 through the BBB (Morris et al. 2019; Enose-Akahata et al. 2012). HTLV-1 tax protein epitope running from amino acid 346–353 unveiled cross-reactivity with a neuron-specific ribonucleoprotein (hnRNPA1); therefore, it develops autoantibodies, and such antibodies have also been detected in sera from HAM/TSP patients (Miner and Diamond 2016; Banks et al. 2001). The in-vitro and in-vivo studies have shown that HTLV-1 infected lymphocytes were able to change the structure of TJs, elevated paracellular permeability, and increased the transcellular migration due to IL-1 α /TNF- α secretion (Futsch et al. 2018). In addition, feline immunodeficiency virus (FIV) exposure triggers impairments in the BBB and choroid plexus (Miller et al. 2012). Caprine arthritis encephalitis virus and Visna virus can also access the BBB by the “Trojan horse” mechanism (Miller et al. 2012) (Fig. 1).

An intricate interaction of flaviviruses with BBB

Japanese encephalitis virus

Several flaviviruses comprise neurotropic and neurovirulent characteristics, namely, Japanese encephalitis virus (JEV), dengue virus (DENV), zika virus (ZIKV), tick-borne encephalitis (TBEV), yellow fever virus (YFV), and WNV (Laureti et al. 2018). It is considered that these viruses enter the brain via a hematogenous route. JEV contributes to BBB disruption by decreasing the expression of claudin-5 and ZO-1. JEV is capable of infecting both BMECs and astrocytes (Liu et al. 2020). Interaction of BMECs with astrocytes is imperative for BBB permeability induced by JEV, which ultimately accelerates the secretion of inflammatory cytokines (Chang et al. 2015). These inflammatory species [i.e., IL-1 β , IL-6, MCP-1, TNF- α , and inducible nitric oxide synthase (iNOS)] are released by microglia and create an environment that debilitates the endothelial barrier (Tohidpour et al. 2017) (Fig. 1). Subsequently, the activated microglia and astrocytes in the CNS of JEV-infected mice robustly produce cytokines: chemokine (C-C motif) ligand 5 (CCL5), C-X-C motif chemokine ligand 10 (CXCL10), chemokine (C-C motif) ligand 2 (CCL2), TNF- α , IL-6, and IFN- γ (Lannes et al. 2017). JEV RNA was detected in mice after 2 days post-infection (dpi) while BBB disintegration was visualized after 4 dpi (Li et al. 2015).

However, the JEV-mediated breakdown of BBB suggests a bystander event rather than a direct virus infection in BBB endothelial cells (Chang et al. 2015).

West Nile virus

WNV infection triggers BMEC-intrinsic expression of inflammatory moieties (type I, type II IFNs, IFN- γ , IL-6, IL-1 β , and TNF- α) at the BBB and eventually disrupts the cohesion among endothelial cells (Kumar et al. 2010) (Fig. 1). An in-vitro exposure of WNV to astrocytes results in the production of matrix metalloproteinases (MMP) that triggers the loss in TJ integrity (Roe et al. 2012). MMPs play a crucial role in WNV neuro invasion as established via a finding that revealed MMP9-/- mice showed resistance toward WNV (Wang et al. 2008). Exposure of human primary brain cortical astrocytes (HBCA) to WNV exhibited overexpression of MMP-1, -3, and -9 while a decrease of a tissue inhibitor of metalloproteinase-2 (TIMP-2) was observed. WNV supernatant when challenged to BMEC exhibited mitigation in the expression level of claudin and ZO-1 (Lazear et al. 2015). Contrarily, the reversed results were observed after the treatment of supernatants with inhibitors of MMP (Lazear et al. 2015). Therefore, it suggests that the production of MMPs induced by WNV may compromise BBB regardless of its infection to the endothelial cells. Notably, studies by Wang et al., and Morrey et al., showed an elevation in the BBB permeability upon exposure of WNV to mice (C57BL/6) (Wang et al. 2008; Morrey et al. 2008). Though it does not trigger any cytopathic effect, however, it alters claudin-1 and increases the level of E-selectin and vascular cell adhesion molecule 1 (VCAM-1) (Mustafá et al. 2019). Numerous pattern recognition receptors (PPRs) recognize the RNA of WNV and elicit innate immune responses. PPR-mediated induction of innate cytokines regulates the permeability of BBB and formation of TJs via proportionate activation of the Rac1 and RhoA (Daniels et al. 2014). It further regulates the transendothelial traffic of the virus. Attenuated type I interferon signalling or interferon induction [Ifnar (-/-) Irf7(-/-)] in mice showed increased BBB permeability and dysregulation of TJs upon WNV exposure (Daniels et al. 2014). Infection of WNV NY strain to mice (C57BL/6) results in upregulation of E-selectin, intercellular adhesion molecule (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) in the brain. Knock-out of ICAM-1 in mice have reduced the leukocyte infiltration via BBB, hence suggesting a decrease in the viral load of CNS (Hallahan and Virudachalam 1997). Several reports suggested that WNV follows a transcellular pathway to get entry into CNS without altering the BBB (Roe et al. 2012).

Zika virus

ZIKV has been detected in the brain of patients suffering from meningoencephalitis and microcephaly. Virus can invade the barrier of the brain by transcytosis (Fig. 1). The BBB model derived from a human-induced pluripotent stem cell (iPSC) revealed infection of ZIKV to infect brain endothelial cells (i-BECs) without creating a disturbance in the BBB barrier cohesiveness or permeability (Alimonti et al. 2018). Although no disintegration to the BBB was detected, post ZIKV infection and the newly generated virions were secreted from the BBB model on the abluminal side and infect the underlying neural progenitor cells (i-NPs) (Alimonti et al. 2018). Notably, i-BEC and i-NPs highly express the AXL (“anexekto” in Greek means “uncontrolled”) which is a presumed ZIKV entry receptor (Alimonti et al. 2018).

Dengue virus

Association of DENV infection with neurological manifestations are still infrequent. In the case of severe dengue (SD), the leakage of plasma was observed in some patients (Li et al. 2017). The first report of DENV infection into brain cells was established using its serotype 2 with the primary cultures of human umbilical vein EC and rabbit cava vein (Calderón-Peláez et al. 2019). Endothelial cell surface-exposed intermediate filament, vimentin (rod domain), is being speculated to be entangled with domain III of its envelope protein (Yang et al. 2016). DENV infection induces Rho-associated coiled-coil-containing kinase (ROCK) reorganization and activation of vimentin which triggers the redistribution of endoplasmic reticulum for an effective viral cycle (replication and assembly) (Lei et al. 2013). In-vitro, by using primary culture and cell lines, DENV-infected endothelial cells were effectively low. DENV-4-infected mouse brain microvascular EC (MBEC) was proportionate to 7 and 12% at 24- and 48-h post-infection (hpi), respectively (Velandia-Romero et al. 2016), while the neuro-adapted D4MB-6 strain infected 50% of the cells at 48 hpi. In addition, activation of endothelial cells upon DENV infection is based on the secretion/expression of sICAM-1 and sVCAM-1 which was observed on the membrane of liver sinusoidal endothelial cells (LSEC) and HMEC-1 (Davies et al. 1993). Infection of D4MB-6 neuro-adapted strain to MBEC triggers expression of E-selectin, PECAM-1, VCAM-1, and ICAM-1 (Calderón-Peláez et al. 2019). Interestingly, the secretion of immune molecules by EC relies on different serotypes of DENV, e.g., DENV1 trigger the secretion of chemokine (C-X-C motif), ligand 1 (CXCL1), CCL2, CCL5, CCL20 IL-6, and TNF- α (Calderón-Peláez et al. 2019). Previous reports also suggested that the reaching of DENV4 in brain parenchyma is fatal, and its

infection accelerates damage to neurons. Also, DENV4 was detected in serum, and the viral titer was higher in cerebrospinal fluid (CSF), suggesting a rapid virus entry through BBB (Calderón-Peláez et al. 2019). All the aforementioned molecules linked with enhanced endothelial permeability and amendments in the coagulator balance related to hemorrhages and dispersed intravascular coagulation were seen during SD (Calderón-Peláez et al. 2019).

Yellow fever virus

The neurovirulence of YFV has been usually evaluated using laboratory neuro-adapted strains and by intracerebral inoculation in mice. IFNA and/or IFNLR mice are more vulnerable to YFV infection. IFNAR^{-/-} mouse showed high viremia and viral load in numerous organs like the kidney and spleen, but it remained same with time. IFNAR-dispersed mice not only showed reduced weight but also unveiled clinical manifestations (Erickson and Pfeiffer 2013). In contrast, IFNAR and IFNLR (ifnar^{-/-}, ifnlr^{-/-}) null mice succumb to YFV infection (Mustafá et al. 2019). In the aforementioned mice models, the permeability of BBB was detected after 5 dpi, while the presence of the virus was observed at 3 dpi (Erickson and Pfeiffer 2013). Thus, it poses the question of whether the disruption of BBB disruption is essential for the invasion of virus.

Tick-borne encephalitis

Yet, another virus, TBEV, is also known to manifest neurological disorders from mild meningitis to severe encephalomyelitis (Bogovic and Strle 2015). Various in-vitro analyses have estimated the virus cytopathic nature, efficient replication, and dissemination in neural cell lines and primary human neurons. Astrocytes are also prone to TBEV replication, though astrocytes are resistant to virus-mediated cytopathic effects. TBEV infects the primary astrocytes of rats persistently and no cellular toxicity was observed until 14 days (Ghita et al. 2021). TBEV infection affects cells in culture at a lower frequency, despite that the activation of astrocytes markedly showed upregulated response of glial fibrillary acidic protein (GFAP), an inflammatory cytokine, chemokines, and MMP-9 (Fares et al. 2020). Therefore, these results pointing toward the astrocyte exposed with TBEV affects the BBB permeability and ultimately the secretion of proinflammatory cytokines (type I IFN) and MMPs (Mustafá et al. 2019). Astrocytes from mice deficient with interferon-alpha/beta receptor (IFNAR) have nullified IFN response by using neutralizing antibodies and made mouse astrocytes more vulnerable to its infection (Lindqvist et al. 2016), whereas the infection with TBEV did not alter the expression and localization of TJ proteins along with adhesion molecules (Palus et al. 2017).

Association of BBB breaching with several other viruses

DNA viruses such as MAV-1 and HSV-1 have been reported to directly make amendments in the structure as well as in the function of BBB (Spindler and Hsu 2012). Adenoviruses enter and replicate after interacting with its receptor coxsackievirus and adenovirus receptor (CAR) which is a known TJ integral protein (Coyne et al. 2007). Nascently packed viruses come out from the basolateral surface and interact with CAR again and ultimately break the TJ to escape apically (Hou et al. 2016). HSV-1-mediated encephalitis obtains high morbidity which contributes to the aggravated immune response due to leukocyte infiltration (Michael et al. 2020). HSV-1 exposure to the murine model induces secretions of CXCL1 and CCL2 chemokines in the brain (Michael et al. 2020). Dispensing of CCL2 receptor in mice showed lower recruitment of monocytes, indefinite viral replication, and increased morbidity, whereas mice deficient with CXCL1 receptor have lower neutrophil recruitment, reduced BBB permeability, and morbidity without affecting the viral load (Michael et al. 2020). Astrocytes produce CXCL1 after inoculation with HSV-1 and CXCL1 is also crucial for neutrophil trans endothelial migration which corresponds to the breakdown of BBB. Thus, the CXCL1-CXCR2 axis depicts a plausible therapeutic target for HSV-1 mediated encephalitis (Michael et al. 2020). Moreover, EBV is also known to be involved with several neurological diseases but the mechanism of BBB crossing is not clear (Rani et al. 2023; Patra et al. 2023) (Fig. 1).

Besides, Reno virus are also known to insult TJ proteins for taking entry into the ependymal and neuronal cells by using junctional adhesion molecules (JAM) (Michalíková et al. 2017). Nonetheless, the hepatitis C virus (HCV) uses occluding-5 and claudin-1 as co-receptor for infection of the liver cells. Likewise, BMECs also express HCV receptors. Therefore, BBB permeability provides HCV with an extrahepatic infection target and contributes to neurological modalities (Fletcher et al. 2012). Also, the open reading frame 2 (ORF2) protein of hepatitis E virus (HEV) showed presence in the brain along with spinal cord sections of infected rabbits. After 48-h in-vitro inoculation of HBMCs with HEV showed a decline in TJ proteins. Hence, these reports suggest that the BBB disruption might be a potential mechanism for invasion of HEV into CNS (Tian et al. 2019). Besides, infection with rabies virus (RV) is lethal for humans once it reaches the CNS. Several glycoproteins of RV regulate its pathogenesis by overseeing virus uptake rate and its replication and spread across synapses (Pulmanusahakul et al. 2008). External surface glycoprotein (G) of RV plays a key role in its uptake into neuronal cells (Dietzschold et al. 2005). An Asn₁₉₄ → Lys₁₉₄ mutation in RV G exhibited significant decrease in the internalization time (Dietzschold

et al. 2008). Further, RV interacts at the neuromuscular junction with nicotinic acetylcholine receptors and travels within the motor and sensory axons to the CNS (Davis et al. 2015). Furthermore, the non-classical neurotropic viruses also show neuroinvasion in an age-dependent manner. For instance, chikungunya virus (CHIKV) is known to cause inflammatory arthritis and rarely involved with the neurological disease in adults, although in 2006 “La Reunion Island” CHIKV epidemic exhibited brain invasion (Soumahoro et al. 2011). Further, infection of CHIKV to neonates results various disease conditions like cerebral palsy, flaccid paralysis, seizure disorders, microcephaly, and even death (Mehta et al. 2018).

John Cunningham virus or human polyomavirus 2 (JCPyV/JCV) and DNA tumor virus infect ~80% human population in the early age (Safak and Khalili 2003; Assetta and Atwood 2017). JCPyV primarily infects oligodendrocytes which trigger demyelination of subcortical white matter in the CNS and subsequently stimulate the demyelinating disease like progressive multifocal leukoencephalopathy (PML) in the immunocompromised individuals (i.e., AIDS patients) (Elphick et al. 2004). The foci of JCPyV in the brain are related to blood vessels which can be corroborated with the hematogenous route as the primary site of infection, and eventually, it spread to numerous secondary sites such as kidney, lymphoid tissues, and brain (Chapagain and Nerurkar 2010). Notably, the detection of JCPyV genomic sequences in the brain autopsy samples obtained from immunocompromised patients suggests another site for its latency (Del Valle and Piña-Oviedo 2019). In the brain, this virus replicates into glial cells like oligodendrocytes and astrocytes and enter into these cells by using proteins like serotonin receptor 2A (5-HT_{2A}-R) and β -arrestin (Mayberry et al. 2019). After maintaining the latency into B-lymphocytes, JCPyV can reach into the brain and potentially trigger PML (Harypursat et al. 2020). Reports also suggested the strong correlation of JCPyV entry into neural tissues directly by the choroid plexus (O’Hara et al. 2020). Intriguingly, the epithelial cells of primary choroid plexus express JCPyV receptors and exhibits its susceptibility for the viral infection. Upon entering to CNS, JCPyV may spread from cell to cell along the myelin sheath (Atkinson and Atwood 2020; Delbue et al. 2017). Moreover, coronaviruses, e.g., middle east respiratory syndrome-coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), can potentially infect immune cells and may enter the brain. Thus, it also led to the speculation that SARS-CoV-2 may also enter into the CNS via infected immune cells (Morgello 2020).

Entanglement of neurotropic viruses with multiple sclerosis

The presence of several pathogens has been continuously overserved in MS clinical samples. Pathogens correlated with the generation and exacerbation of MS include viruses, such as herpesviruses, human endogenous retrovirus families, coronaviruses, and bacteria (*Chlamydia pneumoniae*, *Staphylococcus aureus*) (Morgello 2020; Mentis et al. 2017). Nevertheless, to date, no single pathogenic agent is accepted as a causing agent. The involvement of viruses in MS has been speculated by the presence of anti-viral antibodies (CSF, brain tissue, and blood), viral DNA/RNA, and proteins of numerous viruses (Libbey et al. 2014a; Virtanen and Jacobson 2012). Certain common gastrointestinal, upper respiratory and urogenital tract infections also have some correlation with MS worsening (Marrodan et al. 2019). The contribution of different viruses in MS is hypothesized by different mechanisms such as direct viral toxicity, genetic/molecular mimicry, bystander activation, dual T-cell receptor, spreading of epitopes, and viral déjà vu (Fujinami et al. 2006; Donati 2020). MS pathogenesis has been contributed by many viruses, namely, EBV, HHV-6, Varicella-Zoster virus (VZV), Cytomegalovirus (CMV), JCPyV, human endogenous retroviruses (HERVs), HSV-1, and -2 (Virtanen and Jacobson 2012) (Fig. 1). Despite their belonging to different families, these viruses share the potential to alter the expression of host cell genes, dysregulation of the immune system, and disruption of myelin sheath (Fig. 1). Specifically, the ubiquitous prevalence of herpesviruses in adult populations can target neurons directly or indirectly and aid into tissue damage (Jakhmola et al. 2021). These infections remain asymptomatic and maintain lifelong latency in the immunocompetent hosts (Jha et al. 2016), while the reactivation of these viruses continues their replication cycle and results in cytotoxic effects in the virus-challenged cells (Jha et al. 2016).

Retroviruses and multiple sclerosis

The association of MS has been continuously reported in the upregulated reactivity to certain HERVs solely or in synchronization with herpes viruses (Cusick et al. 2013). Exogenous HIV involves in the activation of HERV via toll like receptor-4 (TLR-4) (Browne 2020). This connection was verified from brains of HIV patients through post-mortem and by checking the epitope cross-reactivity in

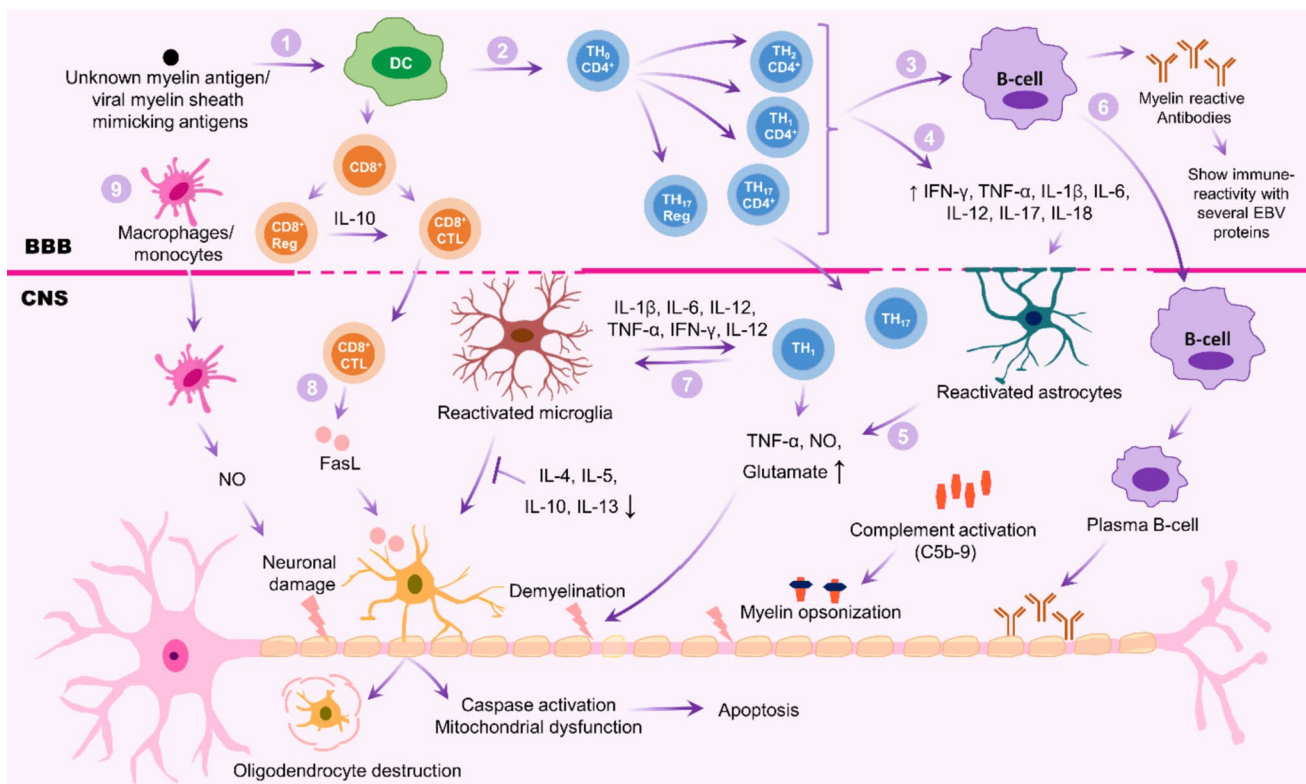


Fig. 2 Antigen presenting cells such as dendritic cells present unknown MS-related antigen/viral myelin sheath mimicking antigens to CD4⁺ T-cells, which in turn become activated and eventually proliferate. These primed CD4⁺ T-cells initiate dendritic cells to activate CD8⁺ T-cells, and their clonal expansion into CD8⁺ regulatory (reg) T-cells and cytotoxic T lymphocytes (CD8⁺ CTL). CD8⁺ CTL can cause direct damage to the myelin layer and axons by releasing several cytokines and pro-apoptotic factors such as FasL. On the other hand, CD8⁺ regulatory cells reduce the inflammatory response by releasing IL-10. Activated CD4⁺ T-cells secrete mainly pro-inflammatory cytokines and also activate B-cells, which produce myelin reactive antibodies. Cytokine interaction with BBB endothelial cells compromises the expression of tight junction proteins such as occludin

and VCAM-1 and alters the activity of matrix metalloproteases. Furthermore, reactivated T-cells in the CNS increase the inflammatory responses. Brain cells, such as microglia and astrocytes, also become activated and release excessive inflammatory cytokines and excitotoxic substances, such as glutamate, nitric oxide (NO). Cytokines and chemokines (CCL2) expressed by microglia increase the infiltration of T-cells and macrophages, respectively. The complement factor, C5b-9, becomes activated, and cause directly damages the myelin sheath. These immune cascades lead to myelin sheath damage, destruction of oligodendrocytes, oligodendrocyte apoptosis, and axonal loss and promote neuronal hyperexcitability leading to the development of CNS neuropathies, such as MS

T-cell responses toward HIV. An uneven ratio of CD8⁺ T-cell and CD4⁺ T-cell was also reported in HIV cases with demyelinating CNS (Stefanou et al. 2019) (Fig. 2). A study by Mameli et al. proposed that EBV activates HERV-W/MSRV/syncytin-1 in astrocytes and peripheral blood-derived cells which hints a possible mechanism involved in MS (Mameli et al. 2012).

Besides, in the blood and/or brain and/or cerebrospinal fluid of MS, the complete virions, RNA, antibodies, gag, and env protein of HERV have been found, and the level of these moieties was associated with status/severity of disease (Morris et al. 2019). The single-nucleotide polymorphisms (SNPs) related to HERV susceptibility toward MS include rs662139 T/C of HERV-W env locus and rs391745 upstream to the HERV-Fc1 locus on the X chromosome,

while SNPs in the tripartite motif-containing (TRIM) protein-encoding genes TRIM5 and TRIM22 showed negative correlation with MS (Morris et al. 2019).

Flaviviruses and multiple sclerosis

Among flavivirus, the non-structural protein, NS1 of ZIKV was detected in microglia by co-labelling with CD11b (Alves-Leon et al. 2019). Microglial role has already been investigated in several arbovirus infections such as dengue, affirming that it fabricates active immune defence during viral infection (Jhan et al. 2017). ZIKV have also showed its extensive presence in the acute disseminated encephalomyelitis (ADEM)-like syndrome and in the MRI lesions of MS (Alves-Leon et al. 2019). Moreover, antibodies against

ZIKV was detected in the plasma (IgM) as well as in the brain biopsy samples (Stone et al. 2020). Besides, WNV is well known to trigger autoimmune diseases like CNS vasculitis with acute stroke and loss of vision. WNV is known to upregulate the both class major histocompatibility complex's (MHC) in the PNS (i.e., Schwann cells) of Lewis's rat (Leis and Stokic 2012). JEV infection into mice triggers demyelination. Reports has revealed the increased proliferation of myelin basic protein (MBP)-primed lymphocytes upon JEV exposure which possibly induce a cascade for deterioration of the axon-surrounding myelin (Tseng et al. 2011). Contrarily, MBP-specific antibodies were also found in some asymptomatic mice which suggests that MBP is not the sole target for myelin autoimmunity. Other myelin proteins (e.g., myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein (PLP)] as well as non-myelin molecules also elicit antibodies in MS patients (Greer 2013).

Herpesviruses and their connection with MS

Alpha herpesviruses

It includes HSV-1, -2 and VZV where the reactivation of VZV was recognized in patients having difficulties in immunosuppressive therapies (i.e., Fingolimod) used for MS (Pfender et al. 2015). VZV DNA levels have also been correlated with the progression of MS specially in patients during the relapse and remission phase of MS (Mentis et al. 2017). Nonetheless, VZV-specific intrathecal IgG was found to be 35-fold higher in patients with MS compared to those with VZV reactivation (Otto et al. 2014). Peripheral lymphocytes derived from MS patients along with control showed that VZV antigens also induce and maintain the activity of HERVs (Mentis et al. 2017). Likewise, the complication faced during immunosuppressive therapy of MS includes HSV-mediated encephalitis which ended up with elevated levels of anti-HSV-1 and -2 antibodies. HSV-1 potentially triggers demyelinating encephalitis in in-vivo models like rat and mice (Duarte et al. 2019).

Beta-herpesviruses

CMV and HHV-6 are β -herpesviruses where the CMV infection is considered as an opportunistic reactivation in MS patients which ultimately leads to MS exacerbation (Sehrawat et al. 2018). Contrastingly, numerous studies revealed a negative correlation between the seropositivity of CMV with MS (Grut et al. 2021). Meta-analysis of 1341 MS patients and 2042 controls is however unable to draw an association between CMV infection and MS (Pakpoor et al. 2013). Indeed, numerous studies supported a link between MS pathogenesis and HHV-6. Neurotropism of HHV-6 has been observed as an accelerated prevalence of viral proteins

and nucleic acid in CSF and MS relative to healthy individuals (Yao et al. 2009). Intriguingly, HHV-6 protein U-24 shares sequence homology with MBP and activates immune cross-reactive T-cells; however, it is pointing toward the molecular mimicry mechanism (Tejada-Simon et al. 2003). In addition, CD46 act as a receptor for HHV-6, and the absence of CD46 in rodents while widely expressed in the common marmoset makes them a potent model organism for MS and for studying the HHV-6 infection mechanism (Komaroff et al. 2020).

Gamma herpesviruses

EBV is known to be involved in numerous neurological modalities. The prevalence of EBV seropositivity in MS patients is approximately 99% (Meier et al. 2021). History of infectious mononucleosis and CSF-confined EBV-specific oligoclonal bands (OCB) is significantly high in patients suffering from MS (Castellazzi et al. 2014). A cohort study with a mean follow-up of 7 years on 147 clinically isolated syndrome (CIS) patients and 50 controls demonstrated immune responses against EBV, HHV-6, CMV, and measles (Lünemann et al. 2010). The aforementioned study also revealed an elevated immune response toward EBNA1. Thus, it suggests that the IgG titer of EBNA1 can use as a prognostic marker for the conversion and progression of the disease (Lünemann et al. 2010). The discrepant presence of EBV in MS lesions suggested that EBV-containing memory B-cells possibly lose the episomic EBV DNA during the replication process, although it hangs on to forbidden epitope recognition which is likely to activate a molecular mimicry mechanism (Laurence and Benito-León 2017). Numerous mechanisms have been proposed in favor of EBV involvement with MS, namely, immune cross-reactivity of the virus with myelin proteins, antibody, and complement system-dependent cytotoxicity and generation of auto-immune responses against alpha-crystallin (Füst 2011). The association of EBV with MS is well explained by a “two-hit hypothesis,” where the primary EBV infection would disrupt BBB and allow the activated immune cells to enter the CNS (Mohammed 2020). Besides, there are shreds of evidence suggesting an association of EBNA2 with neurological ailments, e.g., MS. EBNA2 can accelerate the expression of various host genes and signal recruitment of transcription activations factors such as immunoglobulin kappa J region (RBPJ) and the vitamin D receptor (VDR) (Ricigliano et al. 2015; Jog and James 2021). The above-stated factors are found to be playing a pivotal role in the pathology of MS.

Furthermore, an in-vitro study by Jha et al. has manifested that EBV effectively infects neuroblastoma (i.e., SH-SY5Y and Ntera2) as well as primary neuronal cells (Jha et al. 2015). Another study from our group have shown EBV infection to U-87 MG cells and suggested EBV aids to

neuroinflammatory reactions by increasing proinflammatory cytokines (IL-6, and TNF- α) and also through peripheral blood mononuclear cell (PBMC) infiltration (Jakhmola and Jha 2021) (Fig. 2). Notably, the presentation of recombinant human MOG (rhMOG) by EBV-infected B-cells to CD8⁺ T-cells has been observed (‘T Hart et al. 2013). The higher expression of CD40 on B-cells from the relapsing patients of MS suggests increased antigen presentation by B-cells. Additionally, the EBV-infected B-cells were actively found in demyelinating lesions of relapsing–remitting multiple sclerosis (RRMS) patients who died of lethal relapse (Serafini et al. 2017). Also, the EBV (e.g., EBNA3A and EBNA3C) immortalized memory B-cells were undetectable through patrolling of T-cells by blocking B-cell differentiation into plasma cells by making a connection with the tumor suppressor genes (Styles et al. 2017). An increased titer of anti-EBV antibodies instigates the development of more contrast-enhancing lesions in magnetic resonance imaging (MRI) and higher disability scores (Höftberger and Lassmann 2017). The authors have also reported an opposite association between IgM against viral capsid antigen (VCA) and inflammatory activities (Höftberger and Lassmann 2017). Moreover, the presence of EBV DNA in the CSF of MS patients was also linked with elevated contrast-enhancing lesions (Virtanen and Jacobson 2012). Post-mortem analysis of white matter tissues of MS patients exhibited upregulation of inflammatory cytokine, i.e., IFN- α along with RNA positivity of EBV proteins was detected. In animal models, EBV-containing B-cells regulate the migration of lymphocytes via MS-related markers, namely, EBV-induced gene 2 (EBI2) and an orphan G-protein-coupled receptor. EBI2 activation by oxysterols (7- α -25-dihydroxycholesterol) regulates myelin development and effectively inhibits the secretion of pro-inflammatory cytokines, disruption of BBB, and microglial activation (Rutkowska et al. 2017). However, the infection of EBV stimulates the innate immune responses and further aggravates MS lesions (Guan et al. 2019).

Multiple sclerosis and other additional viruses

The peripheral infection with lymphocytic choriomeningitis virus (LCMV) developed in this virus-specific CD8⁺ T-cells invade the brain and induces neurological manifestation in mice (Matullo et al. 2011) (Fig. 2). Regardless of immune-mediated invasion, the virus enhances the replication of other viruses. For instance, the EBV-infected lymphoblastoid and Burkitt’s lymphoma cell lines showed enhanced torqueto virus (TTV) replication which indicates the communication between two viruses (Borkosky et al. 2012). Likewise, the increased autoantibodies of measles were detected in the serum and CSF of MS patients which suggests dependency with the age and duration of the disease. Canine distemper

virus triggers demyelinating leukoencephalitis which can be used to generate animal models for MS (Attig et al. 2019). Human coronaviruses (HCoV) are significantly known to cause infections in the upper respiratory tract and are also involved with the neurological disease’s initiation/aggravation. Furthermore, single T-cell analysis from MS patients showed HCoV-229E/MBP cross-reactive which implies a molecular mimicry mechanism (Bordeianu 1980).

Animal model use for understanding the pathogenesis of multiple sclerosis

Autoantigen-induced experimental autoimmune encephalomyelitis

Among these models, the most extensively studied is EAE, where the autoimmunity toward CNS is induced in the susceptible mice by immunizing them with myelin protein antigens (Constantinescu et al. 2011). Then, pertussis toxin (PT) and Freund’s adjuvant (CFA) are administered to generate the humoral immune response and develop transient symptoms of relapsing–remitting diseases, similar to MS (Procaccini et al. 2015). Demyelinating experiments have been performed on animal species like guinea pigs and monkeys, yet, rats and mice were proven to be good models to understand the relapsing–remitting and chronic progressive EAE through immunogenetic and acute monophasic (Constantinescu et al. 2011). Different genetic background mice (SJL/J, C57BL/6 and NOD) have been used as an EAE model by eliciting immune responses upon exposure to protein and peptide or can be by passive transfer of encephalitogenic T-cells (Table 1) (Miller and Karpus 2007). This immune response-generating immunogen can be derived from CNS proteins, namely, MBP, PLP, or MOG. An epitope of PLP₁₃₉₋₁₅₁ induces relapsing–remitting disease in mice (SJL/J), while the chronic nature diseases are generated upon challenge to immunodominant MOG₃₅₋₅₅ peptide concomitant administration of PT in C57BL6/J mice (Table 1). Auto-immune reactions are also induced by neurofascin (NF-155), contactin-2, NF-186, neurofilament-M, and S100 calcium-binding protein B (Midroni and Ashby 1989; Baumann and Pham-Dinh 2001; Derfuss et al. 2009). Relapsing–remitting EAE (RR-EAE) could also be developed by passive transfer of PLP-reactive T-cells, after then immunization of donor mice with PLP epitopes, subsequently, the isolation of peripheral lymphoid cells and subsequent transfer into naïve recipient (Table 1).

Virus-induced chronic demyelinating diseases

Numerous epidemiological studies have suggested that infections with several neurotropic viruses may elicit an immune-

Table 1 Enlistment of multiple sclerosis models can be generated by exposure to myelin peptides, viruses, and toxins. The mechanism to generate mice model and its underlying mechanism involved and its application

S. no.	Models for multiple sclerosis	Mechanisms	Applications	References
1	EAE in SJL/J mice	Immunization with PLP ₁₃₉₋₁₅₁	For studying neuroinflammation	(Bebo et al. 1996; McRae et al. 1992)
2	EAE in C57BL/6J mice	Inoculation with MOG ₃₅₋₅₅	For studying neuroinflammation	(Bittner et al. 2014)
3	EAE in NOD mice	Immunization with MOG ₃₅₋₅₅	For studying immune system activation	(Ignatius Arokia Doss et al. 2015)
4	Relapsing remitting-EAE	Administration with PLP/MBP epitopes or PLP reactive T-cells	For studying immune system activation	(Miller and Karpus 2007)
5	TEMV-mediated MS	Infection with GDVII and TO subgroups of TEMV	For studying the inflammation-induced demyelination	(Oleszak et al. 2004)
6	Influenza-inoculated C57BL/6 mice	EAE and influenza infected comorbid mouse	Neuroinflammatory autoimmune disease influences lung immunity	(Glenn et al. 2017)
7	Samiriine herpesvirus	Immunization with the viral peptide “AAQRRPSRPFA”	For studying autoreactive responses	(Gautam et al. 1998)
8	Cuprizone-induced MS	Chelates copper and targets mature oligodendroglia cell death with demyelination	For studying demyelination and remyelination processes	(Torkildsen et al. 2008)
9	Lysolecithin-mediated MS	Demyelination in the focal areas by activating the phospholipase A2	For studying demyelination and remyelination processes	(Plemel et al. 2018)

mediated response in the brain. These viral infections of the brain induce degradation of myelin sheath in mice; thus, it includes picornavirus, such as TMEV and a few coronavirus strains, i.e., MHV (Biswas et al. 2016). TMEV indicated as a neurotropic viral infection model for MS is divided into two subgroups, GDVII and TO, as per their potential to cause disease in the brain. GDVII subgroup strains, namely, GDVII and FA, can induce death in mice within 2 weeks indicating their high neurovirulence in mice (Table 1). TMEV TO subgroup strain includes BeAn8386 (BeAn) which commonly causes acute polio encephalomyelitis (Procaccini et al. 2015; Gautam et al. 1998) (Table 1). Notably, TMEV triggers this progressive inflammatory demyelinating only in mice and not in other different species, unlike EAE. Predominant infection of GDVII virus to neurons was observed during paucity in the recruitment of inflammatory mononuclear cell (MNC) (Oleszak et al. 2004). Contrary to infection of GDVII, CD3⁺ T-cells and parenchymal, perivascular, and subarachnoidal mononuclear cells (MNC) infiltrate in the gray matter of CNS during the acute phase of Daniels strain of TMEV (DA) infection (Tsunoda and Fujinami 2010). Additionally, MS and its animal model (EAE) are believed to be generated via severe inflammatory demyelination followed by axonal damage where lesions get generated from the outside (myelin) to the inside of the axon and depicted as outside-in model (Libbey et al. 2014b), whereas, the case of TMEV infection to neurons leads to an inside-out model of demyelination, and the disrupted axons spread was observed during the early phase of infection which eventually

develops in the chronic phase (Sato et al. 2011). Therefore, these evidences pointing toward the degeneration of axons induced by the infiltration of macrophages and T-cells into the brain ultimately trigger myelin loss.

To get deeper knowledge about EBV involvement with MS, animal models are in use where mice infected with murine gamma herpesvirus shows EAE upon induction (Hassani and Khan 2022). Likewise, gamma-herpesvirus callitrichine herpesvirus 3 (CalHV3) naturally infects marmosets and CalHV3 immortalized B-cells like EBV (Fujiwara and Nakamura 2020). The CalHV3-infected B-cells behave as APCs for MHC class II and MHC class I to CD4⁺ and CD8⁺ T-cells, respectively. CalHV3 model shows a conversion from tolerogenic destructive processing of MOG peptide to productive processing and auto-aggressive T-cell activation ('t Hart 2020). Notably, the serum examination of MS patients unveiled that EB nuclear antigen 1 (EBNA1) 411–426 epitopes with antibodies cross-react with MBP (Jog et al. 2020). EBNA1 411–426 peptide inoculation in SJL/J and Balb/c mice develop signs of EAE (Jog et al. 2020). Besides, the L2 protein peptide from human papillomavirus (HPV) is overlooked by an MBP-specific T-cell clone from an MS patient and MBP-specific autoantibodies purified from MS brain tissue (Campos and Ozbun 2009). HPV-7 motif with the sequence “VHFFK” is similar to MBP aa87–99 suggesting molecular mimicry (Ruiz et al. 1999). This viral peptide induces papillomavirus-specific SJL mouse T-cells

that cross-react with MBP aa87-99 which majorly is an encephalitogenic epitope for SJL mice (Falk et al. 2000). Histopathology of CNS and cytokine profiles of papillomavirus peptide-specific encephalitogenic T-cells showed similarity as induced by MBP (Ufret-Vincenty et al. 1998). Therefore, it signifies the aspects of self-antigen recognition and a cross-reactiveness of viral peptides by human, and murine MBP-specific T-cell receptors are conserved (Martinsen and Kursula 2022). A herpesvirus *Saimiri* (HVS) peptide (AAQRRPSRPFA) shares homology to MBP peptide 1–11 (ASQKRPSQRHG) and can set off a panel of MBP aa1-11-specific T-cell hybridomas and eventually leads EAE in mice (Table 1). These low doses of viral peptide-specific T-cell lines were highly encephalitogenic. The authors have also demonstrated the possibility of cross-recognition of these peptides by TCRs which can potentially lose the T-cell tolerance to self-antigens in autoimmune diseases employing cross-reactivity with unrelated peptides (Gautam et al. 1998).

The infection of CMV in mice with the expansion of CD4⁺CD28^{-/-} T-cells has exhibited an aggravation of inflammation, myelin sheath disruption, and worsening of the EAE symptoms (Vanheusden et al. 2017). The intranasal exposure of HHV-6A and HHV-6B to non-human primates showed MS-like neuroinflammatory disease, EAE (Leibovitch et al. 2018). The viral antigens of HHV-6 in virus/EAE marmosets manifested remarkable elevation in the brain lesions (Constantinescu et al. 2011). Augmentation in the EAE was also observed upon exposure to the HSV-1 vector expressing IL-5 (Nygårdas et al. 2011). After being challenged with virus R8316 (IL-5), the authors have observed improvements in the disease score which counts on the cumulative disease index and the EAE mortality rate (Nygårdas et al. 2011). The above-mentioned vector of HSV-1 triggers an increase in the type-1 IFN response in CNS, especially IFN- β . Indeed, both type I and type II IFNs influenced the regulation and inflammation in MS along with neuromyelitis optica in EAE (Danastas et al. 2020). Further, the inoculation of 2D2 mice with influenza A virus also showed clinical and histological EAE in ~ 29% of mice. Subsequently, the mice adapted influenza A virus showed that almost 90% of CD4⁺ T-cells in 2D2 mice express MOG aa35–55-specific-TCR and neurofilament-m (NF-M18–30); very few (4%) develop spontaneous classic EAE (Bettelli et al. 2003). Cumulatively, the influenza A virus can activate glia and has been correlated with increased relapse risk in MS patients (Blackmore et al. 2017). Nonetheless, another study used two different EAE rodent models to elucidate murine gammaherpesvirus-68 (+ MHV-68) ability in worsening of neurological symptoms (Flaño et al. 2002). SJL mice inoculated with UV inactivated + MHV-68 or intranasal + MHV-68 in due course immunization

against PLP peptide aa139-151 (Peacock et al. 2003). The + MHV-68-mediated complications was due to remarkable viral replication within the CNS, and infectious-center assays signify no detectable virus in the brains and spinal cords of infected rodents undergoing EAE (Peacock et al. 2003).

Toxin-induced demyelination

Moreover, the toxin-generated animal models are mainly used to study the demyelination and remyelination processes. Among the most commonly used agent, cuprizone (bis-cyclohexanone-oxaldihydrazone) chelates copper and targets mature oligodendroglia cell death with demyelination, which have paramount effect on the astrocytes and microglial activation (Table 1) (Procaccini et al. 2015; Flaño et al. 2002). Deficiency of copper induces metabolic failure, and the exact reason it targets oligodendrocyte is still a question of debate (Emerson et al. 2001). Nonetheless, lysolecithin induces demyelination in the brain by subsiding the destruction to the adjacent cells (Procaccini et al. 2015). Injection of lysolecithin into the spinal cord of animals (cat, rabbit, rat, and mouse) induces demyelination in the focal areas by activating the phospholipase A2 (Table 1) (Wallace et al. 2003). Toxin induced degradation of myelin sheath because of detergents' primary toxic effects instead of secondary effects on oligodendrocytes (Procaccini et al. 2015; Peacock et al. 2003).

Conclusion

Neurotropic viruses disrupt the homeostasis of the BBB and enters into the brain parenchyma through diverse number of routes where they trigger or aggravates the neurological diseases. Viruses act on the CNS by weakening the BBB integrity and exhibiting the molecular mimicry against host proteins which generates autoimmune responses and ultimately the MS. Animal models for MS (EAE) can aid in the detailed understanding of mechanism behind numerous devious strategies of viruses for their involvement in the brain diseases. Therefore, the neurotropic virus association with BBB leakiness and MS is crucial, and certain viral proteins can potentially be targeted therapeutically.

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Declarations

Competing interests The authors declare no competing interests.

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