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Neuropathogenesis of Neurotropic Viruses

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ABSTRACT

Neuropathogenesis can simply be defined as the mechanisms of the origin, development and progression of the CNS disease which comprises both neuroinvasion and neurovirulence. Viruses that have the ability to induce neuropathogenesis are called neurotropic pathogens. The exact mechanisms of neuropathogenesis is still unknown, however, the following pathways have been proposed and include retrograde axonal transport, hematogenous spread from the peripheral blood to the cerebral blood vessesls across blood brain barrier, direct invasion of the endothelial cells and endocytosis across the viral receptors. The main neurotropic viral families are picornaviruses, arboviruses, paramixoviruses, arenaviruses and herpes family viruses. In this review, the main mechanisms of neuropathogenesis of the neurotropic members of these viral families was discussed.

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Introduction

Viral infections of the central nervous system (CNS) have been demonstrated as the causative agents in many chronic debilitating diseases such as neurodegenerative diseases, neuroinflammatory diseases, meningoencephalitis or CNS malignancies. Therefore, a better understanding of the mechanisms underlying the pathways of viral-induced immunopathology, neurodegeneration, neurotoxicity and neuroinflammation is necessary in order to achieve effective therapeutic measures [1]. Moreover, a good understanding of the disease pathogenesis along with the precise elucidation of the viral and host genetic determinants that facilitate viral CNS invasion is critical in order to develop novel strategies against viral CNS infections [2].

Neuropathogenesis can simply be defined as the mechanisms of the origin, development and progression of the CNS disease. The process comprises of both neuroinvasion which is the ability of the virus to enter CNS, and neurovirulence which is the ability of the virus to cause CNS disease. The viruses that have the ability to induce neuropathogenesis are called neurotropic pathogens and they penetrate the brain by many mechanisms which include retrograde axonal transport along motor and olfactory neurons, haematogenous spread across the blood–brain barrier (BBB), blood–cerebrospinal fluid barrier, meningeal–cerebrospinal fluid barrier, via direct infection of endothelial cells or via spread of infected leukocytes across the BBB into the brain parenchyma [3].

In this review a focus was made on neurotropic viruses from wide range of different viral families and we extensively discuss their viral-induced neuropathogenic mechanisms, the viral and host factors related to neuroinvasion, neurotropism and neurovirulence have been fully elaborated herein. A complex picture on the development of the CNS disease from the point of infection to the occurrence of clinical signs and symptoms was also given. The paper informs scientific community the critical mechanisms involved in the development of brain diseases for future therapeutic targets.

Pathogenesis

Picornaviruses

Enteroviruses (EVs) are diverse group of heterogeneous viruses with most of the members causing mild signs and symptoms such as fever, rashes or rhinitis [4].

However, some EVs penetrate CNS resulting in many different manifestations including meningitis, encephalitis, meningoencephalitis, paralysis or ataxia [5].

The precise mechanism of these clinical manifestations is unknown, however, some pathways through which these viruses invade CNS and virus-host cell interactions have been described. The primary route of infection is GI tract from where it is spread to the CNS. For polio virus many routes of CNS entry have been postulated. It was shown to penetrate CNS through neuromuscular junction, transport of viral particles from the muscle to the CNS also known as retrograde transport model, receptor-dependent retrograde and receptor-independent axonal transport processes and ability to cross the blood-brain barrier and directly invade brain microvascular endothelial cells. For other non-polio EVs retrograde axonal transport system has been described as the main neuropathogenesis [6].

Many studies suggested the role of white blood cells (WBCs) as carriers in transporting neurotropic viruses from the blood to the brain. For instances monocytes were shown to be carrier of polio viruses from the blood to the nervous system, cocksackie viruses infect blood-derived Mac-3+ mononuclear cells which

then migrate to the CNS, EV71 infect various immune cells such as cluster differentiation 14 (CD14+) cells, dendritic cells, and peripheral blood mononuclear cells (PBMCs) which could then spread to the CNS. Also, echoviruses were shown to have the propensity of infecting dendritic cells. However, the evidence supporting all these is largely poor [5,6].

Moreover, the role of receptors in mediating the entry of neurotropic viruses into the CNS has been demonstrated by many studies. For instances, CD155 which is a receptor found in many tissues of brain, GI tract, kidney, skeletal muscles, lungs and liver was shown to mediate entry of polio virus into these target tissues, whereas human decay-accelerating factor (DAF, CD55) was used as a receptor for entry into the CNS by echoviruses and coxsackie B viruses, however, not all coxsackie B viruses [4,6].

Another receptor called coxsackievirus and adenovirus receptor (CAR) is used by both coxsackie and adenoviruses for entry into the CNS [6].

Many receptors were demonstrated to mediate the entry of EV71 into the CNS which include scavenger receptor B2 (SCARB2), P-selectin glycoprotein ligand-1 (PSGL-1), annexin A2 (Anx2), sialylated glycan, dendritic cell- specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN), and heparin sulfate [4].

Despite being immunologically inactive zone, EVs infection can stimulate immune responses in the CNS. Upon the entry into the CNS, EVs cause lymphocytes or monocytes infiltration, depending on the type of the EV, with generation of pro-inflammatory cytokines and chemokines with interleukins and tumor necrotic factors resulting in neuro-inflammation, damage of adjacent brain tissues by the TNF and increase vascular permeability by the IFN-gamma. Depending on the viral tropism, these immune processes will consequently lead to meningitis, encephalitis, meningoencephalitis or paralysis [4,6].

However, some studies suggested that viral induced apoptosis was the main neuropathogenesis of EVs infections with MicroRNAs (miRNAs), newly discovered class of small non-protein coding RNAs that act via endogenous RNA interference that mediate the post-transcriptional regulation of more than 30% of animal genes , playing a critical role in reducing this mechanism [7].

Human Parechovirus (HPeVs) infection commonly infect children under 5yr and mostly cause mild clinical symptoms but occasionally is associated with severe neurological manifestation like meningitis, encephalitis, encephalomyelitis or acute flaccid paralysis with HPeV3 causing more severe neurological diseases especially in neonates [8,9].

The different types of HPeVs show different cell tropism with HPeV 1 growing in cell culture more easily than HPeV 3 which is usually isolated serologically from CSF. Infections with HPeVs types 1,2,4-6 are established through arginine-glycine-aspartic acid (RGD) motif located in the C terminus of the capsid protein VP1 by its attachment to cell surface integrins. However, HPeV3 infection is established via different receptor pathway that is independent of RGD, unfortunately this pathway is still unknown [8,9].

This mechanism of host cell recognition by RGD motif and cell-cell and cell-matrix interactions is the main neuropathogenesis of HPeVs [10].

Arboviruses

The mode of transmission of arboviruses could be human to human transmission following blood transfusion or organ transplant, or in some cases transplacentally from mother to fetus [11].

However, the commonest mode of transmission of arboviruses is through a bite from an arthropod vector carrying infectious pathogens that is introduced either directly to the host blood via the proboscis of the vector which pierces blood capillaries producing viremia that spread hematogenously to the brain tissues [12].

Another route is by infecting the dendritic (Langerhan) cells of the skin dermis following viral inoculation by the vector where it multiplies, and then these infected dendritic cells migrate to the draining lymph nodes through lacerated capillaries where another viral replication occurs. The viruses then enter blood stream via lymphatic and thoracic ducts [11,13,14].

From the blood, the virus may enter the bone marrow, spleen or liver to form secondary amplification or may disseminate directly from the blood to the brain tissues [12,15].

Many mechanism have been suggested by which the virus enter CNS by crossing BBB [1].

In one mechanism it is described that the viruses in the blood stream first infect PBMCs and it then replicate in the endothelial cells of the cerebral capillaries or in the striated muscles surrounding BBB and in so doing it disrupt the integrity of the BBB by damaging the endothelial cells which is responsible for maintaining the integrity of the BBB. The infected PBMCs are then introduced from circulation into the brain tissues via disrupted BBB [12].

In another mechanism, it is suggested that virus enter the CNS by endocytosis via the olfactory bulb or the choroid plexus as seen in JEV and WNV 15].

Also, passive transfer of the virus across the BBB carried by the infected leucocytes has been suggested especially in cases of high viremia [11,12,13,15].

Following entry into the CNS, the infected PBMCs stimulate immune responses with activation of numerous cytokines resulting in the neuroinflammation and damage of the brain tissue in cerebral cortex, basal ganglia, brainstem, cerebellum, and occasionally spinal cord with consequent clinical manifestation depending on the viral tropism and type of the arboviruses [15].

Alternatively, the virus may directly infect the brain tissue causing damage or disruption in neuronal circuitry of the brain, or it may induce apoptosis of the neuronal cells triggering cascade of events that damages the neuronal tissue [11,12,13].

This explains why arboviruses are captured in brain tissue during autopsy. Shortly after entry into blood stream, many viruses including arboviruses stimulate release of interferons (IFNs) and cytokines by the host innate immune system which curtail the viral infection by identifying and subsequent clearance of the viral components. To counteract these immune responses, the arboviruses develop both structural and non-structural proteins that antagonize the host IFN response and therefore establishes infection [16].

Paramixoviruses

Mumps virus infection is highly contagious that only affect humans and the mode of transmission is by direct contacts, air droplets, infected formites or oral contact with infected respiratory droplets or secretions. The incubation period is about three weeks with contagious phase commencing 1 to 2 days prior to the onset of signs and symptoms. Following inoculation, the virus multiplies in the upper respiratory tract mucosa which usually localized there but occasionally spreads to the regional lymph nodes from where it disseminates systemically to the various body organs [17,18].

Experimental studies on animal suggest the neuroinvasive nature of mumps where it enters CNS via choroid plexus or through passive transport of infected mononuclear cells across BBB during viremia. Within the cerebrospinal fluid (CSF), the virus spread throughout the ventricular system and multiplies in the ependymal cells lining the ventricles. Virus can then invade the brain parenchyma where it infects pyramidal cells of the cerebral cortex and hippocampus producing many clinical manifestations. Following viral replication, the ependymal cells becomes inflamed, degenerate and shade into the CSF causing aqueductal stenosis and subsequent hydrocephalus. As CSF communicates freely with perilymph, the viral shedding into the CSF results in the transmission of the virus into the inner ear structure causing sensorineural deafness [17].

Measles is primarily transmitted via respiratory route through contact with infected individuals. It is highly contagious with incubation period of about two weeks. Following viral inhalation in the air droplet, the virus goes to its early targets cells which include CD11c+ myeloid cells (which is likely an alveolar macrophages) and dendritic cells (DCs) in the lungs and respiratory submucosa [19,20].

Virus is then spread primarily to the bone marrow and thymus, secondarily to the spleen, tonsils, lymph nodes, and then bronchus-associated lymphoid tissue (BALT) as tertiary dissemination because they are rich in CD150+ lymphocytes which together with nectin cell adhesion molecule 4 (nectin-4, previously also known as poliovirus receptor-related 4 or PVRL4) constitutes the main receptors for MV in many tissues. The mechanism of viral entry into the CNS is not fully understood, however, it has been suggested that viral entry is via passive transport of the infected lymphocytes from circulation into the brain tissue as BBB under normal circumstance allows passage of lymphocytes [19,20].

Following entry, the infected lymphocytes cause infection of the vascular endothelial cells which subsequently infect neuronal cells resulting into many neurological manifestations including acute disseminated encephalomyelitis (ADEM), measles inclusion body encephalitis (MIBE) or subacute sclerosing panencephalitis (SSPE) through mechanism that is largely unknown. In some cases, persistence of this CNS measles infection is observed usually due to mutation of measles virus or restriction of viral gene expression at translational or transcriptional levels causing failure of eliminating MV infected brain cells [19,20,21].

The mode of transmission of Henipaviruses is via contact with infected horses (for HeV), pigs (NiV) or feeds contaminated by bat feces or urine. Transmission can also be through respiratory secretions or aerosols [22].

Following inoculation of the virus, it goes to the respiratory epithelium where it induces inflammatory responses with cytokines stimulation leading to Acute Respiratory Distress Syndrome (ARDS)-like disease [23].

From respiratory epithelium, viral replication then spreads to the lungs endothelium, spleen, kidney or brain with consequent viremia and, in some cases, multi-organ failure [23,24].

The entry of the virus into the brain is facilitated by the expression of CD6, a ligand for the activated leukocyte cell adhesion molecule ALCAM (CD166) on the microvascular endothelial cells of the the blood-brain barrier, which serves as a binding side for henipaviruses. This mediates hematogenous passage of the virus into the CNS. Also, entry of Henipaviruses into the CNS anterogradely via the olfactory nerve has been reported [22].

Within the microvascular endothelial cells, the virus stimulate inflammatory responses with production of TNF-α and IL-1β which further disrupt the BBB and further facilitate the viral entry into the CNS. The inflammatory cells also induce neuronal injury through mechanism that is largely unknown resulting to many clinical manifestations such as encephalitis, vasculitis, thrombosis or parenchymal necrosis among others [25].

Arenaviruses (lymphocytic choriomeningitis virus)

LCMV has an extensive viral replication and the outcomes of infection depends on the route of transmission and the strain of the virus. Clinical presentation occur as a result of exaggerated host immune response against the viral invasion instead of direct cytopatic effect of the virus [26,27].

Mode of transmission to human is usually by inhalation of aerosolized urine and drop¬pings of infected rodents. Transmission can also occur transplacentally with severe effects on infants or after solid organ transplant. Many mechanisms that underlie the neuropathogenesis of LCMV have been proposed as summarized by Zhou et al as follows: 1. LCMV-specific mechanical distension / edema / compression that is inflammation-mediated and CD8+ T cell-dependent. 2. Release of chemical mediators. 3. LCMV-specific CD8+ T cell-mediated killing or cytotoxicity [27].

It has been established in experimental model that viral inoculation into the CNS result into activation of CD8+ T cell mediated inflammatory response inside the virus-infected CNS that mediates destruction of the blood-brain and blood-CSF barriers [26].

This responses were shown to be mediated by T cell recognition of its target via major histocompatibility (MCH) class I and II molecules, and consequently produce severe inflammation of the leptomeniges, the choroid plexus and the ependyma lining the ventricles with partial sparing of the brain parenchyma and the cellular infiltrates seen were macrophages and CD8+ T lymphocytes, which is mainly virus-specific CD8+ T cells constituting about 90% [26,27,28,29].

Herpes Family Viruses

Herpes simplest viruses are very common worldwide with two main serotypes: herpes simplex virus (HSV) type 1 (HSV-1) and HSV type 2 (HSV-2). About 90% of adult HSV infection is caused by HSV-1 with HSV-2 causing seropositivity in about 20-25% of cases [30,31].

HSV-1 is commonly found in the oral mucosa and ocular areas whereas HSV-2 is commonly isolated in the epithelial lining of the genital tract, however, HSV are the commonest cause of sporadic encephalitis. Majority of HSE is caused by HSV-1 but when infection is acquired prenatally as in neonates, HSV-2

become the predominant cause and it constitutes about 10% of all HSV infections [30,32].

There are different ways by which the virus enter CNS. If the mode of transmission is via cutaneus inoculation from flank, footpad, or oral mucosa, viral replication is usually limited to the site of inoculation and therefore infection become localized with less risk of encephalitis. But, if the inoculation is intravenously as during blood transfusion or organ transplant, viral replication takes place in the liver and systemic infection ensues with great risk of encephalitis. Intravaginal, intraocular or intranasal inoculation result in CNS invasion by the virus. Intravaginally the virus spread from the vaginal epithelia to the dorsal root ganglia, spinal cord neurons and then CNS. Intranasally and intraocularly, the virus spread from nasal or ocular epithelia to the CNS via retrograde axonal transport along the trigeminal (TG) neurons as contact exist between the nasal epithelium and eye with the sensory termini of TG neuron [32,33].

In the soma of the sensory neurons, the virus undergoes genomic transformation where it expresses a single transcript, LAT, and several microRNAs. The LAT RNA prevent apoptosis of the neuronal cells and this preserve the viral genome [32,33].

The virus then develops many antiviral mechanisms thereby maintaining the viral survival in the neuronal cells. First, the virus develop an anti-autophagy mechanism by expressing certain proteins from microRNAs called infected cell protein (ICP) gene products, ICP34.5 and ICP47 [30].

Antiviral innate immune responses by type 1 interferon (IFN-1) is also counteracted by expressing another protein during viral replication called infected cell protein (ICP) gene products, ICP0 [30,32].

Therefore, the IFNs activate natural killer cell (NK) AND T-cell responses which critically attempt to clear the virus but in so doing, they induce inflammatory damage to the neuronal cells.
Also, some mechanism of countering innate immune responses have been proposed by some scholars. For example, autosomal defect of intracellular protein UNC93B1 has been shown to cause impairment of cellular IFN I responses leading to failure of innate immunity against the virus [32,34].

Also, single-gene errors in Toll-like receptor 3 (TLR3)-IFN I pathways has been demonstrated to cause impaired innate immune responses. Once into the brain tissue, the virus has tropism for temporal and frontal lobe, however, it occasionally affects brain stem. The resulting pathology is largely due to exaggerated inflammatory responses against the viral invasion by the proinflammatory cytokines, NK and IFNs [30,32].

The pathogenesis of VZV starts with the viral inoculation in either epithelial cells of the mucous membranes through air droplets or in the skin via contact with infected skin. The virus undergoes replication at the site of primary inoculation producing high viral titre locally. Because of this high infectious viral titre, dissemination occurs either by infecting local T cells which then carries the virus to the various organs including lungs, liver and brain or the virus may undergo retrograde axonal transport to the nearby sensory ganglia [35].

Within the sensory ganglia, the virus may undergo latency or multiply several times resulting in extensive inflammation and necrosis. Antiviral mechanisms are also developed by the virus which prevent its clearance by the immune system. This is achieved by expressing certain proteins, which are largely unknown, that down-regulate MHC-1 expression on fibroblasts and T cells and as such the virus cannot be recognized by CD8+ T cells. It also blocks expression of MHC –II on IFNs which causes failure of antiviral innate immunity by mechanism that is poorly understood. Many research have now reported vasculopathy of the cerebral blood vessels as the main neuropathogenesis of VZV CNS infection rather than encephalitis resulting in many clinical manifestations including spinal cord infarction, aneurysm, subarachnoid and intracerebral haemorrhage, cranial nerves diseases and peripheral artery disease. This vasculopathy is a result of the extensive inflammation and necrosis produced due to rapid viral replication [35,36].

EBV infection is also common worldwide with two distinct strains infecting humans, EBV-I and EBV-II. The infection occurs through epithelial cells of the oropharynx and of the cervix as well as resting B lymphocytes via CD21 molecule as the viral receptor on the epithelial cells and B lymphocytes. Inoculation of the virus on the epithelial cells result in to viral replication and active infection whereas viral inoculation on the B lymphocytes do not produce viral replication and therefore result into latent infection. Latent infection is stimulated by certain chemicals or antibodies leading to the expression of certain gene products called ZEBRA (Z EBV replication activator) protein, which acts as a trigger of viral replication in latency [37].

The B cells then transform into Ig-producing B cell blasts by expressing the Epstein-Barr nuclear antigens (EBNA) 1, 2, 3A, 3B, 3C, and LP and the latent membrane proteins (LMP) 1, 2A, and 2B [37,38].

This blast B cell is tightly control by Cytotoxic T lymphocyte cells (CTLs) to prevent development of lymphoproliferation [39].

The blast B cell then migrate to the tonsils where it will continue to express EBNA1, LMP1, and LMP2 with resultant conversion of blast B cell to memory B cell which leave the tonsils to the blood and circulate freely. This memory B cells when return to the tonsils initiate replicative transcriptional program that produces infectious viruses which infect new B cells [38].

These immunologically silent B cells (memory cells) are transported to the brain via cerebral blood vessels, within the CNS these B cells produce pathogenic auto-antibodies which stimulate inflammatory responses leading to the neuroinflammation and consequently neuronal damage [39].

Human cytomegalovirus (HCMV) infection affects all individuals from neonate to adults across the world and first identified in stillbirth in 1910 and then during organ transplant in 1964 [40]. The mode of transmission can be from direct contact with infected individual via kissing or sexual intercourse, nosocomial via blood transfusion or organ transplant or transplacentally from mother to fetus causing congenital CMV. HCMV infection is generally asymptomatic in a healthy individual as immune responses against HCMV antigen is more robust than in any other viral infection but tend to be severe with fatal consequences in immunocompromised patients [40,41].

Following infection, the virus undergo latency in the body lymphocytes only to be reactivated when the immunity is compromised as in HIV patients, organ transplant recipients or patients receiving immunosuppressive drugs [40].

Within the body, the viral components are recognized by Toll-like Receptors(TLRs) which initiate innate immune responses against the virus and this lead to the production of inflammatory cytokines, such as type1 interferons (IFN), tumour necrosis factor alpha (TNF-α) and interleukin-6(IL-6). These inflammatory cytokines then activate phagocytic cells like dendritic cells, which engulf HCMV-infected cells. Natural killer (NK) cells are also recruited which eliminate HCMV-infected cells by the release of cytotoxic proteins, which destroy target cells. This explain immune responses in early control of HCMV infection [40,42].

During reactivation or occasionally during primary infection the virus develops an antiviral mechanisms against immune responses by expressing certain proteins through its microRNAs called UL 16 and UL 142 proteins which bind with ULBP1, ULBP2 and MICB ligands of NK cells [41]. This binding activates NKG2D receptor which prevent the expression of NK cell activating ligands on the surface of infected cells and therefore render the NK cells unable to detect host viral infected cells [40,42].

Another mechanism is the expression by the virus of a homologous human cytokine, IL-10 which help the virus in suppressing anti-cytomegalovirus immunity. HCMV also expresses anti-apoptotic proteins, UL 36 and UL 37 which prevent apoptosis of infected cells and thus promoting its dissemination within the host. Little is known about the mechanism by which HCMV enters into CNS due to limitations in studying human subjects, however, elaborate explanation has been offered by studying murine CMV in mice [41,42].

CMV may gain access to the CNS via many routes which include virus induced disruption of BBB, passive transport across BBB of the infected lymphocytes from circulation into the brain tissue or axonal transport across olfactory nerve [42].

Within the brain, the virus start replication and this stimulate immense host immune responses with activation of numerous inflammatory cells resulting to neuroinflammation and unintended damage of the brain tissue leading to the observed clinical manifestations [43].

Conclusion

Viral infections of Central Nervous System have become emerging public health problem as it is associated with serious morbidity and mortality. Infections with wide range of neurotropic viruses may cause localized or diverse neuropathology with consequent development of acute or chronic neurological manifestations. The viral ability to infect humans, enter into the nervous system and causing damage is clearly a complex interactions of different factors ranging from the viral genomic constitution, host genetic make up and immune status, viral mobility and ability to attach to the host tissues to the viral affinity to certain host tissues and its capacity to stimulate the host immune responses. In this review, a current view on the viral and host factors implicated in the neuropathogenesis of the major neurotropic viruses from different viral families was provided and a highlight of the main mechanisms in which the viruses enter CNS, breech the protective barriers of the nervous system, stimulate host immune responses with consequent development of neurological diseases was gieven.

This review has some limitations as only published data were used and restricted only on the neuropathogenesis of neurotropic viruses without discussing the virology and epidemiology of these viruses. However, where applicable, explanation of the viral genomic factors that promote neuropathology was provided. As the exact mechanism of viral neuropathology is still unknown, further studies are therefore needed.

References

1. Soldan SS, Jacobson S (2010) Viral infections of the central nervous system: pathogenesis to therapeutics. Journal of Neuroimmune Pharmacology 5: 267-270.
2. Häusler M, Schaade L, Kemeny S, Schweizer K, Schoenmackers C, et al. (2002) Encephalitis related to primary varicella-zoster virus infection in immunocompetent children. Journal of the neurological sciences 195: 111-116.
3. Ludlow M, Kortekaas J, Herden C, Hoffmann B, Tappe D, et al. (2016) Neurotropic virus infections as the cause of immediate and delayed neuropathology. Acta neuropathologica 131: 159-184.
4. Muehlenbachs A, Bhatnagar J, Zaki SR (2015) Tissue tropism, pathology and pathogenesis of enterovirus infection. The Journal of pathology 235: 217-228.
5. Xiao X, Qi J, Lei X, Wang J (2019) Interactions between enteroviruses and the inflammasome: new insights into viral pathogenesis. Frontiers in microbiology 10.
6. Huang HI, Shih SR (2015) Neurotropic Enterovirus Infections in the Central Nervous System. Viruses 7: 6051-6066.
7. Ho BC, Yang PC, Yu SL (2016) MicroRNA and Pathogenesis of Enterovirus Infection. Viruses 8:11.
8. Westerhuis BM, Koen G, Wildenbeest JG, Pajkrt D, de Jong MD, et al. (2012) Specific cell tropism and neutralization of human parechovirus types 1 and 3: implications for pathogenesis and therapy development. Journal of General Virology 93: 2363-2370.
9. Benschop K, Wildenbeest J, Pajkrt D, Wolthers K.(2012) Human Parechoviruses, new players in the pathogenesis of viral meningitis. InMeningitis IntechOpen.
10. Stanway G, Hyypiä T (1999) Parechoviruses. Journal of virology 73: 5249-5254.
11. Davis LE, Beckham JD, Tyler KL (2008) North American encephalitic arboviruses. Neurologic clinics 26: 727-757.
12. Perng GC, Chen WJ (2013) Arboviral Encephalitis. InEncephalitis IntechOpen.
13. Hollidge BS, González-Scarano F, Soldan SS (2010) Arboviral encephalitides: transmission, emergence, and pathogenesis. Journal of neuroimmune pharmacology 5: 428-42.
14. Atkins GJ (2013) The pathogenesis of alphaviruses. ISRN Virology 2013: 22.
15. Lim SM, Koraka P, Osterhaus AD, Martina BE (2011) West Nile virus: immunity and pathogenesis. Viruses3: 811-828.
16. Hollidge BS, Weiss SR, Soldan SS (2011) The role of interferon antagonist, non-structural proteins in the pathogenesis and emergence of arboviruses. Viruses 3 :629-658.
17. Rubin S, Eckhaus M, Rennick LJ, Bamford CG, Duprex WP (2015) Molecular biology, pathogenesis and pathology of mumps virus. The Journal of pathology 235: 242-252.
18. Hviid A, Rubin S, Mühlemann K. Mumps (2008) The Lancet 371: 932-944.
19. Laksono BM, De Vries RD, McQuaid S, Duprex WP, De Swart RL (2016) Measles virus host invasion and pathogenesis. Viruses 8: 210.
20. Schneider-Schaulies, Volker ter Meulen, Sibylle Schneider-Schaulies J (2001) Measles virus interactions with cellular receptors: consequences for viral pathogenesis. Journal of neurovirology 7: 391-339.
21. Schneider-Schaulies S, Liebert UG (1991) Pathogenetic aspects of persistent measles virus infections in brain tissue.

InSeminars in Neuroscience 3: 149-155.

22. Escaffre O, Borisevich V, Rockx B (2013) Pathogenesis of Hendra and Nipah virus infection in humans. The Journal of Infection in Developing Countries 7: 308-311.
23. Rockx B, Brining D, Kramer J, Callison J, Ebihara H, et al. (2011) Clinical outcome of henipavirus infection in hamsters is determined by the route and dose of infection. Journal of virology 85: 7658-7671.
24. Selvey LA, Wells RM, McCormack JG, Ansford AJ, Murray K, et al. (1995) Lavercombe PS, Selleck P, Sheridan JW. Infection of humans and horses by a newly described morbillivirus. Medical Journal of Australia 162: 642-644.
25. Wong KT. Nipah and Hendra (2010) viruses: recent advances in pathogenesis. Future Virology 5: 129-131.
26. Thomsen AR (2008) Lymphocytic choriomeningitis virus-induced CNS disease: A model for studying the role of chemokines in regulating the acute antiviral CD8+ T-cell response in an immune privileged organ. Journal of Virology.
27. Zhou S, Halle A, Kurt-Jones EA, Cerny AM, Porpiglia E, (2008) Lymphocytic choriomeningitis virus (LCMV) infection of CNS glial cells results in TLR2-MyD88/Mal-dependent inflammatory responses. Journal of neuroimmunology 194: 70-82.
28. Fousteri G, Dave Jhatakia A (2019) Viral infections and autoimmune disease: roles of LCMV in delineating mechanisms of immune tolerance. Viruses 11: 885.
29. Zhou X, Ramachandran S, Mann M, Popkin D (2012) Role of lymphocytic choriomeningitis virus (LCMV) in understanding viral immunology: past, present and future. Viruses 4: 2650-2669.
30. Kollias CM, Huneke RB, Wigdahl B, Jennings SR (2015) Animal models of herpes simplex virus immunity and pathogenesis. Journal of neurovirology 21: 8-23.
31. Kopp SJ, Ranaivo HR, Wilcox DR, Karaba AH, Wainwright MS, et al. (2014) Herpes simplex virus serotype and entry receptor availability alter CNS disease in a mouse model of neonatal HSV. Pediatric research 76: 528.
32. Mancini M, Vidal SM (2018) Insights into the pathogenesis of herpes simplex encephalitis from mouse models. Mammalian genome29: 425-445.
33. Steiner I, Kennedy P. G.(1995) Herpes simplex virus latent infection in the nervous system. Journal of neurovirology 1: 19-29.
34. Goodman JL, Engel JP (1991) Altered pathogenesis in herpes simplex virus type 1 infection due to a syncytial mutation mapping to the carboxy terminus of glycoprotein B. Journal of virology 65: 1770-1778.
35. Arvin AM (2000) Varicella-zoster virus: pathogenesis, immunity, and clinical management in hematopoietic cell transplant recipients. Biology of Blood and Marrow Transplantation 6: 219-230.
36. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA (2009) Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. The Lancet Neurology 8: 731-740.
37. Straus SE, Cohen JI, Tosato G, Meier J (1993) Epstein-Barr virus infections: biology, pathogenesis, and management. Annals of Internal Medicine 118: 45-58.
38. Pender MP (2011) The essential role of Epstein-Barr virus in the pathogenesis of multiple sclerosis. The Neuroscientist 17 :351-367.
39. Meier UC, Giovannoni G, Tzartos JS, Khan G (2012) Translational Mini-Review Series on B cell subsets in disease. B cells in multiple sclerosis: drivers of disease pathogenesis and Trojan horse for Epstein–Barr virus entry to the central nervous system?. Clinical & Experimental Immunology 167: 1-6.
40. Griffiths P, Baraniak I, Reeves M (2015) The pathogenesis of human cytomegalovirus. The Journal of pathology 235: 288-297.
41. R Schleiss M (2011) Congenital cytomegalovirus infection: molecular mechanisms mediating viral pathogenesis. Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorder 11: 449-465.
42. Krmpotic A, Bubic I, Polic B, Lucin P, Jonjic S (2003) Pathogenesis of murine cytomegalovirus infection. Microbes and Infection 5: 1263-1277.
43. Cheeran MC, Lokensgard JR, Schleiss MR (2009) Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. Clinical microbiology reviews 22: 99-126.