

VIRAL INFECTIONS OF THE CNS: THE UNRAVELING OF THE MYSTERY

Mageshbabu Ramamurthy^a, Sathish Sankar^a, Ilakkiya Arumugam^b, Balaji Nandagopal^a, Padma Srikanth^{b*}, Sridharan Gopalan^a

^aSri Sakthi Amma Institute of Biomedical Research, Sri Narayani Hospital and Research Centre, Sripuram, Vellore - 632 055, Tamil Nadu, India

^bDepartment of Microbiology, Sri Ramachandra University, Porur, Chennai - 600 116 Tamil Nadu, India

ABSTRACT

Infections of the central nervous system (CNS) caused by viruses are of public health importance. Viral infections in CNS have always been a challenge to the treating physician. The pathogenesis of viral infection is complex and the determinants include virus, host and environment which are responsible for their varied clinical presentations. The disease manifests differently in immunocompetent and immunosuppressed individuals. Several DNA and RNA viruses are known to have neurotropism with site specificity. Immunogenetics of the host plays an important role in disease outcome. Viral transmission may occur through arthropods, animal bites,

human to human contact, oral, vertical and even cannibalism or consumption of raw bush-animal meat. Certain viral infections resolve with neurological sequelae that include cognitive, motor and sensory deficits while certain others are linked with autoimmune diseases. The evolving technologies and advancements in biomedical science will aid in unraveling the mystery behind these viral diseases.

Key Words: Acute and Chronic CNS infections, neurotropic viruses, Slow viruses.

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INTRODUCTION

There are several mysteries in the biosphere. The origin of viruses/prions is a mystery on their own. The theory of origin of viruses include the development of obligate intracellular parasitism from independent microorganism with loss or no biosynthetic capacity, a process called “reductive evolution” of an agent(s). Imagine the Chlamydia-like energy dependent parasite losing its biosynthesis machinery. Mitochondria of mammalian origin could be the progenitor of mammalian viruses. Further, the discovery of giant viruses like Pandoravirus is a mystery on its own. It has been suggested that comets carrying protein building blocks, water and infectious nucleic acid materials could have implicated as influencing evolution of viruses. For the last 40 years, we have known of the ability of self replicating protein infectious material (prions) which strangely is a mutant form of normal cellular protein. Many viruses and prions have the ability to wreak havoc in the central nervous system (CNS) in humans and animals. How and what happens in this process is the mystery and this is at several levels.^[1]

The interactive triangle of pathogenesis consists of the three main participants in the malady; the virus, host and environment is shown in Fig. 1. Certain viruses of the DNA and RNA groups as well as infectious proteins cause

neuropathology and neurological diseases. Usually a small proportion of infected humans develop neurological disease (with varying outcomes) and the subsequent mortality. The disease is differently manifested in immunocompetent and immunosuppressed individuals.^[2]

The blood-brain barrier (BBB) is highly selective in its permeability and acts as a barrier between blood and the brain. Anatomically BBB is a cellular barrier, formed by tight junctions between the brain endothelial cells. The BBB allows the passage of water, some gases, and lipid-soluble molecules by passive diffusion, as well as the selective transport of molecules such as glucose and amino acids that are crucial to neural function. Astrocytes and pericytes are necessary to create the BBB. A few regions in the brain, including the circumventricular organs, do not have a BBB. In the major ventricle of the brain there is a choroid plexus (CP) through which the normal physiological fluid viz. cerebrospinal fluid (CSF) is filtered out into the ventricles. This CSF circulates in the ventricular space and between the meninges, the brain, brain stem and spinal cord nourishing the CNS areas. Certain infections produce inflammation in the CP which results in increase in inter cellular spaces because of inflammation causing observable abnormal changes, this is when you see inflammatory cells including lymphocytes in the CSF and pathogens. Non bacterial meningitis; aseptic meningitis caused by viruses’ results in increase in lymphocytes. There is specific activation of B and T cells with documentation of intrathecal specific immunoglobulins (antibodies). Only after the resolution of the infections, do CSF parameters return to normal (glucose, protein, cells) it should be emphasized here that the CNS is an immunologically privileged site so is inherently free of inflammatory cells.^[3]

CORRESPONDING AUTHOR

Dr. PADMA SRIKANTH*

Professor, Department of Microbiology

Sri Ramachandra University, Porur

Chennai - 600 116.

Email ID: srikanth_padma@rediffmail.com

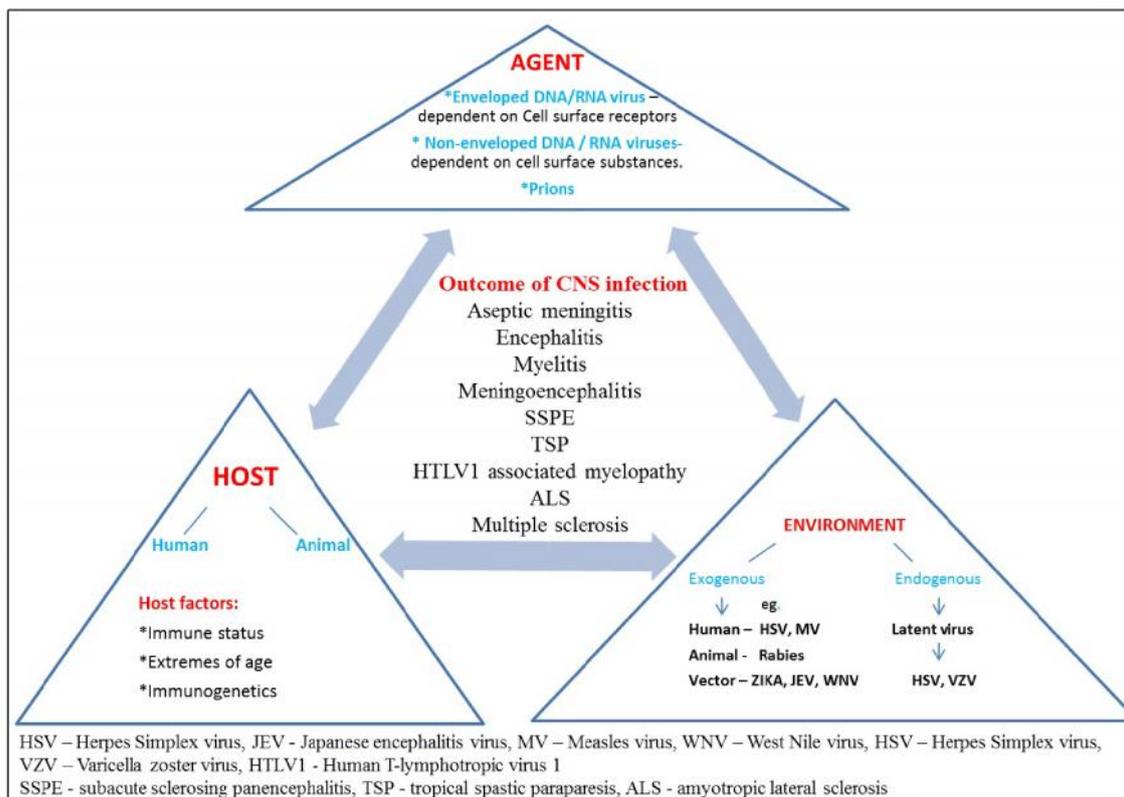


Fig 1. THE INTERACTION OF HOST ENVIRONMENT AND VIRUS IN PATHOGENESIS OF CNS VIRAL INFECTIONS

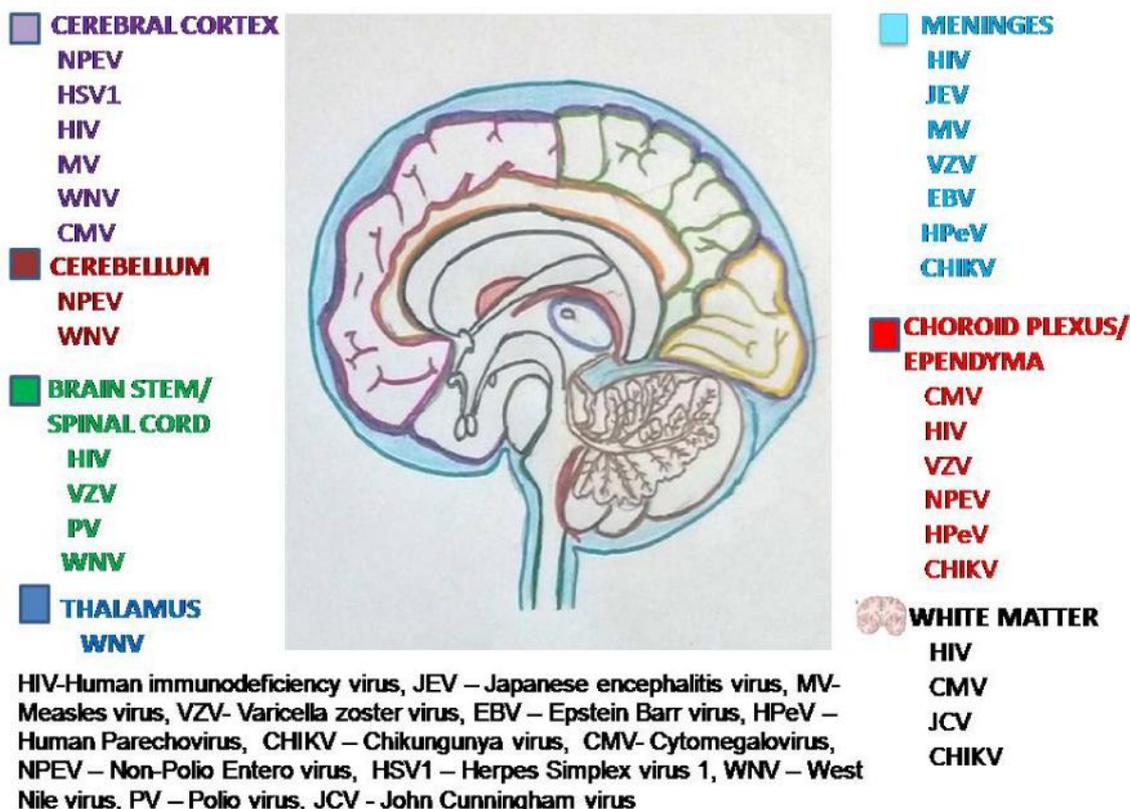


Fig 2. NEUROTROPISM OF VIRUSES TO DIFFERENT PARTS OF THE BRAIN IN THE COURSE OF AN INFECTION

Table 1: Determinants of virus-host interactions in neurotropism

Anatomical sites in the CNS infected primarily by virus	Virus	Virus cell surface receptor	Normal cell function of these receptor molecules	Virus antireceptor (on virus particle)
Meninges, cerebral cortex	Measles Virus	CD46	C3b and C4b inactivation	Heamagglutinin
Brain stem/ Spinal cord	Poliovirus (PV1, 2 and 3)	CD155	Establishes tight contact between epithelial cells	Conformationally changed VP1
Cerebral cortex	Herpes Simplex Virus1	Heparin sulphate	Angiogenesis	Glycoprotein B and C
Brain stem/Spinal cord, Thalamus	Rabies virus	Nicotinic acetylcholine receptor (nAChR)	Neuronal impulse transmission at synaptic junction	Glycoprotein G
Brain stem/Spinal cord, cerebral cortex	Human Immunodeficiency Virus 1	CD4	Co-receptor for APC MHC recognition	gp120/gp41
Brain parenchyma (White matter)	John Cunningham virus (JCV)	5-HT _{2A} serotonin receptor	In CNS plays a role in cognition and memory	VP1

Adapted from Becky Schweighardt and Walter J Atwood **Journal of Neuro Virology**, 7: 187± 195, 2001

VIRAL NEUROTROPISM AND THE HOST

Different viruses with tropism for varying anatomical sites of the brain are shown in Fig.2. Viruses like Human Immunodeficiency Virus (HIV), Japanese Encephalitis Virus (JEV), Measles Virus (MV), Varicella Zoster Virus (VZV), Epstein Barr Virus (EBV), Human Parechovirus (HPeV), and Chikungunya virus (CHIKV) infect meninges; viruses like Cytomegalovirus (CMV), HIV, VZV, Non polio Enterovirus (NPEV), HPeV and CHIKV infect Choroid plexus/ependyma; viruses like JEV, Herpes Simplex Virus -1 (HSV-1), HIV, MV, West Nile Virus (WNV), CMV infect cerebral cortex; viruses like NPEV and WNV infect cerebellum; viruses like HIV, VZV, EBV, Poliovirus (PV), WNV, infect brain stem/spinal cord; viruses like WNV, infect the thalamus; viruses like HIV, CMV, John Cunningham Virus (JCV), CHIKV infect white matter.^[4] This association of certain viruses with given sites of the CNS is not rigid. The message here is multiple viruses can infect the CNS at one or more sites. The viruses in particular, neurotropic viruses, use certain cell surface molecule as receptors to which they bind and this is followed by virus penetration of the cell for naked viruses. The enveloped viruses also are dependent on surface receptors for their binding and usually their envelope fuses with the host cell membrane. It is only

after this step and internalization of the virus particle does replication begin. Examples of neurotropism of viruses and the receptors used by them are shown in Table-1.

The outcome of CNS infection is variable (Fig.1). Viral infection of CNS leads to complete recovery, partial recovery or fatality. It is important to note that all neurotropic virus infections do not lead to clinical disease, majority may be asymptomatic. Case-in-point poliomyelitis/ encephalitis is seen only in 1:300 of infected individuals of PV/JEV.^[5] The interesting feature is polioviruses are transmitted feco-orally and JEV is transmitted by an arthropod vector *Culex* species, it is to be noted that the disease rate is similar for these two neurotropic viruses despite different routes of transmission. PV can cause any of three manifestations: febrile viral illness, aseptic meningitis or poliomyelitis. Variation in clinical outcome is seen even for one given virus circulating in a given geographical area (topotype). One can conjecture that the host may be hence the determinant of the outcome in this situation.

Outcome of the infection is driven by the host factors; immunocompetence and age of the host. In several viral infections the severity is more at the extremes of age (less than 2 years and over 70 years). The immunogenetics of the host plays an important role both in innate immunity

and active (specific) immunity. Toll-like receptors (TLR 3), have been shown in experimental mice to have a protective role against both WNV and JEV infections.^[6,7] Pathogen recognition receptors (PRRs) play a significant role as determinants of first line of defense: Toll-like receptors (TLRs) are part of the system. Others that are part of this innate immune system include: retinoic acid-inducible gene I-like receptors (RLRs), the nucleotide oligomerization domain-like receptors (NLRs) and cytosolic DNA sensors (AIM2), intracellular sensors play a role in the clearance of viruses that replicate in the cytosol of cells.^[8] Mutations of certain host cell surface molecules can affect the ability of the virus to infect cells. HIV is known to use both CD4 molecules as receptors and to efficiently infect cells another co-receptor the CCR5 molecule is used. Europeans who have a deletion mutation of the cell receptor (CCR5-delta 32) are refractory to HIV-1 infection.^[9]

Human Leukocyte Antigen (HLA) haplotypes of host have an important role to play in specific immune response to viruses. Viral T cell antigenic epitopes are presented to CD4+ T cells in the binding groove of Class I major histocompatibility complex (MHC) molecules on non professional antigen presenting cells (APC), almost any infected cell, e.g. tissue fibroblasts including professional APC like macrophages and dendritic cells important for initiating an afferent T cell response generating Cytotoxic T cells (CTL) and memory T cells. Viral epitopes that elicit antibody response are the B cell epitopes which are presented on the professional APC in grooves of MHC Class II antigens with CD4 helper T cell function generating antibody producing plasma cells and memory B cells. Best responses are seen with the epitopes that have high affinity to the host MHC molecules on APC.^[10]

Most cytokines are polypeptide messenger molecules (8-140kDa), and some may also be glycosylated. Their biological function in the context of inflammatory response can be differentiated into four major groups: innate immunity (IL-1, IL-5, IL-6, and IL-8); management of inflammatory processes (IL-1, IL-4, and TGF- β); lymphocyte activation and proliferation (IL-2 and IL-4); and leukocyte growth mediation (IL-1, IL-3, IL-5, and IL-6).

If cytokines are involved in chemical attraction of cells they are referred to as chemokines that can further be split into four major subgroups (CXC, CC, XC, and CX3C) depending on their structural organization of conserved cysteine residues in the amino terminus. A distinct profile of cytokines and chemokines leads to an effective and specific host defense and promotes leukocyte migration during viral CNS infection. During meningitis and encephalitis, an array of cytokines and chemokines has been demonstrated to be regulated including CCL2, CXCL10, CXCL12, IL-1 and TNF- .

THE VIRUSES

Certain viruses or protein infectious particle (prions) exhibit the attribute of neurotropism. Mutation in RNA genome of polioviruses is associated with loss of neurovirulence, changes in nucleotide (nt) sequence of PV1 genome (57nt), PV2 (2nt) and 10nt changes in PV3 are associated with this phenomenon. Likewise, reversion of attenuated strain to neurovirulent PV2 is known.^[11] A high viral RNA in the plasma of HIV infected individuals is associated with symptomatic infection and CNS involvement.^[12] Similarly, this association has been observed in plasma virus load and CNS disease for WNV infection.^[13] Several researchers have shown the detection of multiple viruses in CNS infections especially members of family *Herpesviridae* both in immunocompetent and immunosuppressed individuals. It is difficult to ascribe aetiological significance to the presence of more than one virus in the CSF. It could be postulated that one agent was the primary pathogen and the presence of others could be due to reactivation.^[14,15]

Another feature of certain CNS infecting viruses, especially members of family *Herpesviridae* is their ability to establish latency in the host. Some like HSV and VZV do so in the neuronal cells of the sensory nerves ganglions. The protein kinase (66-pk) of VZV gene 66 phosphorylates IE62 and is a gene of VZV latency. This results in accumulation of IE62 in the cytoplasm and reduces nuclear IE62-induced gene activation and thus keeps the virus quiescent. Using the techniques of reverse transcriptase-dependent nested PCR, DNA sequence analysis, in situ hybridization, and immunohistochemistry researchers have revealed VZV open reading frame 66 in latently infected human trigeminal ganglia associated VZV latency.^[16]

The cellular activity of epigenetic regulation is used by EBV for its different phases of existence in the host cells. EBV exhibits prelatent, latent and lytic phases in the life cycle. By a unique at each phase a certain set of active and silenced viral genes are seen. Epigenetic modifications of viral gene expression are documentable. The transcription factor BZLF1 is important for the switch from latency to the lytic phase. BZLF1 binds to methylated viral promoters and causes epigenetically suppressed genes to be expressed.^[17]

THE ENVIRONMENT

Exogenously acquired animal and human viruses cause disease in humans. Endogenous latent viruses cause disease in immunocompromised host. Many viruses exhibit vector dependence to reach humans. There are differences in tropical, temperate and cold climates in terms of circulation of certain viruses. Competence of vectors and transmission of neurovirulent viruses is an issue to be well understood especially with the emerging threat of Zika virus which is now seen in North and South America as well as in East Asia. Ecological niches of these

agents vary. Some are transmitted via arthropods, some by animal bites, human to human contact, orally, vertically and even cannibalism or consumption of raw bush-animal meat (HIV transmission to humans). The emerging infections result from destruction of forests and subsequent interaction between sylvatic and urban cycles of certain viruses.^[18] Acquisition of certain viruses is shown in Table-2.

IMPORTANT VIRAL INFECTIONS

Important viral infections of CNS, causative agent and its manifestations are shown in Fig.3.

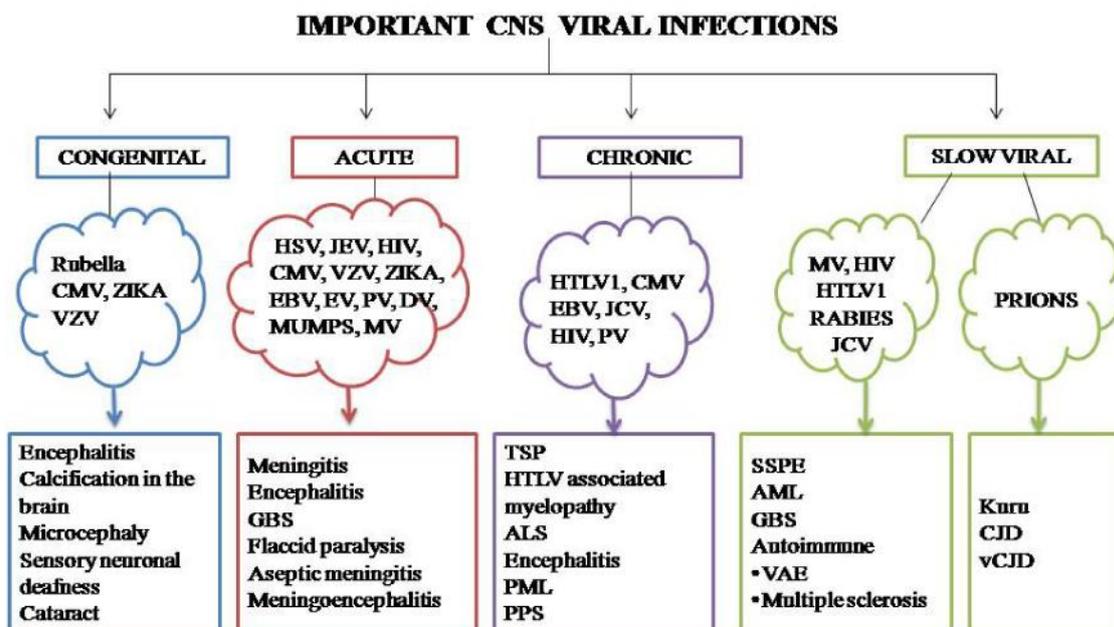
Congenital viral infections: Several viruses are known to be associated with congenital infections of the new born with CNS involvement typically this includes maternal infections transmitted to the fetus by the transplacental route or during delivery, infection happening in the birth canal. Maternal infection with Rubella, CMV, Zika early in pregnancy (i.e fetal morphogenesis) is associated with severe CNS involvement of the new born. The manifestations may be encephalitis, calcification in the brain, cataract, microcephaly or sensory neural deafness.^[19]

Acute CNS infections: Several acute CNS infections manifest with changes in cognitive function, signs of depression, acute motor and sensory changes which will soon be followed within 72 hours of manifestations of CNS disease with classical changes in the biochemistry

and cellular features of the CSF indicative of viral etiology. These include infections with HSV, JEV, HIV, and CMV.^[20] In the case of JEV the virus reaches the CNS by viremic spread or through the olfactory nerves of the cribriform plate of ethmoid like influenza virus.^[21] Another form of viral spread to the CNS and subsequent pathology is seen with VZV. The virus spreads from skin/mucosa into sensory nerve endings. Virus travels to dorsal root ganglion (DRG) and becomes latent. Reactivation occurs with decreased cell-mediated immunity. Initial replication occurs in affected DRG after reactivation.^[22]

Spread of Rabies virus to CNS may take a few weeks to 18 months. It depends on the amount of virus contained in the saliva which is deposited at the site of the bite of an infected animal. It is a fatal disease if post exposure prophylaxis is not given within 7 days of the bite, if the bite is in the limbs. Facial bites by infected animals may lead to rapid development of the disease.^[23]

Retroviral infections of the CNS can occur as an acute or chronic condition. In the case of HIV, Guillain-Barré syndrome (GBS) could be seen as part of acute sero-conversion illness. The virus easily crosses the BBB through cell to cell spread or seeding in the CSF through infected CD4 cells. HIV causes CNS manifestations but this is usually seen with opportunistic pathogens when the individual is immunosuppressed in the course of HIV disease. The virus indirectly destroys cells in the CNS and also causes sustained CNS inflammation, accelerated



HIV-Human immunodeficiency virus, JEV – Japanese encephalitis virus, MV- Measles virus, VZV- Varicella zoster virus, EBV – Epstein Barr virus, CHIKV – Chikungunya virus, CMV- Cytomegalovirus, HSV – Herpes Simplex virus, WNV – West Nile virus, PV – Polio virus, HTLV1 – Human T-lymphotropic virus 1, DV- Dengue virus, JCV - John Cunningham virus, EV – Enterovirus. GBS- Guillain-Barre Syndrome, TSP- tropical spastic paraparesis, ALS – amyotrophic lateral sclerosis, PML- progressive multifocal leukoencephalopathy, PPS – post-polio syndrome, SSPE – subacute sclerosing panencephalitis, VAE – vaccination allergic encephalomyelitis, CJD – Creutzfeldt-Jacob disease, vCJD – variant CJD

Fig.3. Important Viral infections of central nervous system

Table-2: Important neurotropic viruses: Their geographical distribution, transmission and their potential to cause congenital infections

Virus	Geographical distribution	Transmission	Potential for congenital infections	CNS manifestations	Nature of spread
HSV	Global	Close personal contact, sexual, respiratory and genital routes	Perinatal infections are known for HSV2/ HSV1	Encephalitis, meningoencephalitis	Sporadic
VZV	Global	Close personal contact, respiratory route	Perinatal infections are known	Encephalitis, meningoencephalitis	Sporadic
Rubella	South Asia, Africa	Close personal contact, respiratory route	Congenital infections are known	Encephalitis, meningoencephalitis, retinitis, sensory neural deafness, mental retardation	Sporadic/ Outbreak
CMV	Global	Close personal contact, respiratory route and vertical transmission	Congenital infections are known	Encephalitis, ventriculoencephalitis, transverse myelitis, polyradiculomyelitis	Sporadic
Zika virus	S. America, N. America, S. E. Asia	Mosquito <i>Aedes spp</i> , vertical and sexual	Congenital infections	Brain ischemia, myelitis, meningoencephalitis	Epidemic
WNV	N. America	Mosquito <i>Aedes spp</i> , <i>Culex spp</i>	Nil	Meningoencephalitis, encephalitis, myelitis	Epidemic
JEV	Asia	Mosquito <i>Culex Spp</i>	Nil	Encephalitis, meningoencephalitis	Outbreak/ Epidemic
Non-polio enterovirus	Global	Feco-oral route	Neonatal sepsis	Polio-like illness, encephalitis	Outbreak/ Epidemic

vascular disease with amyloid deposition.^[24]

The Enterovirus genus includes over 100 serotypes/genotypes. At least 20 are known to cause CNS infections. The conditions range from acute flaccid paralysis (AFP) to polio-like-illness. AFP caused by NPEV generally improves to restoration of motor functions unlike permanent sequelae with infections of polioviruses. Both PV and NPEV enter through the mouth, replicate in the pharynx, GI tract and local lymphatics. From here there is a hematogenic spread to the CNS. Viral spread along nerve fibers could cause destruction of motor neurons.^[25]

GBS is post infectious sequelae marked by demyelination which could be localized or ascending. An acute inflammatory demyelinating polyradiculo neuropathy (AIDP) with acute motor-sensory axonal changes is a subtype of GBS.^[26] The viruses associated include EBV, VZV, CMV, Dengue viruses, Zika virus.

Systemically and locally released pro-inflammatory cytokines (IL-1 β , TNF, IL-6) are responsible for demyelination.

Chronic CNS infection other than slow viral diseases: HTLV-1 is usually associated with adult T cell leukemia but has been implicated in certain neurological conditions like tropical spastic paraparesis (TSP)/ human T-lymphotropic virus (HTLV-1) associated myelopathy (HAM), amyotrophic lateral sclerosis.^[27] In addition CMV and EBV are known to establish chronic encephalitis in immunosuppressed patients. EBV is associated with chronic fatigue syndrome in the Northern hemisphere. Here the virus is known to transiently appear in the CSF compartment of the CNS.^[28]

Progressive Multifocal Leukoencephalopathy (PML) is a condition caused by John Cunningham Virus (JCV). Here there is asymmetric involvement brainstem and is

Table 3: Slow viral and Prion infections of Humans

Disease	Agent	Host(s)	Incubation period	Nature of Disease
SSPE	MV	Humans	2-20yrs	Chronic sclerosing panencephalitis
PML	JCV	Humans	Years	CNS demyelination
PRPE	Rubella virus	Humans	Years	Chronic encephalitis
Kuru	Prion	Humans	Months to years	Spongiform encephalopathy
Creutzfeldt-Jacob disease (CJD)	Prion	Humans	Months to years	Spongiform encephalopathy
vCJD	Prion	Bovine, Humans	Months to years	Encephalitis, myelitis

seen more commonly in AIDS patients. In non HIV infected patients who have T-cell immunodeficiency, lymphoproliferative disorders chronic granulomatous diseases, solid organ transplant recipients or hematologic malignancy PML could also be seen.^[29]

Post polio syndrome (PPS) is seen several years after polio affliction. A possible mechanism for PPS is motor neuronal loss due to reactivation of a persistent latent virus. Muscle atrophy and denervation is seen, foci of perivascular and interstitial inflammatory cells have been found in 50% of biopsies of patients with PPS. Activated T cells and immunoglobulin M and immunoglobulin G antibodies specific for gangliosides also have been found. Another possibility is an infection of the polio survivor's motor neurons by another enterovirus (Acute Flaccid paralysis agent) that is different from the one responsible for the patients' polio condition.^[30]

SLOW VIRAL INFECTIONS

SSPE: Measles is an acute febrile exanthematous condition that is usually a self-limiting disease, but it can be associated with several complications, one of which is subacute sclerosing panencephalitis (SSPE) which manifests several years later. Rapid replication of MV that has been quiescent for years is triggered by some reactivation event(s) and results in hyper-reactive immune responses. Demyelination in persistent MV infections is due to a complex combination of viral cytopathic effects on neuronal cells and immune-mediated mechanisms. The pathogenesis of persistent MV infection in SSPE is not very clear.

Prions in CNS disease: These agents cause variety of human and animal disease. Certain form of animal prion disease is transmissible to humans. The pathogenic prion protein is a mutant form of a normally expressed protein

in low amounts in the host cells. The protein is very stable to moist heat. The normally expressed protein is different from the prion protein seen in disease. Certain features of slow viruses' and prion diseases are shown in Table-3. Table-4 shows differences between the normal cellular prion protein and the pathological prion protein. Variant Creutzfeldt-Jacob disease (vCJD) is a rare degenerative fatal brain disorder. It was reported in the year 1995. It was believed to be due to ingestion of beef products contaminated by prion agent a variant of bovine spongiform encephalitis producing agent. Early psychiatric symptoms and sensory symptoms are much more common here and cerebellar findings are present in all patients with vCJD.^[31]

Table-4: Differences between cellular and scrapie proteins

Attribute	PrP ^c	PrP ^{sc}
Solubility	Soluble	Non soluble
Structure	Alpha-helical	Beta-Sheeted
Multimerisation state	Monomeric	Multimeric
Infectivity	Non-infectious	Infectious
Suceptibility to proteinase K	Susceptible	Resistant

PrP^c: normal cellular expressed prion protein (low level)

PrP^{sc}: pathological protein expressed in disease- scrapie protein (high level)

Amyotrophic lateral sclerosis (ALS): A progressive, invariably fatal neurologic disorder resulting from upper and lower motor neuron degeneration. This condition typically develops during the sixth or seventh decade of life, and is diagnosed based on standard clinical criteria. A small percentage of persons infected with the HIV-1 or HTLV-1 develop ALS-like syndromes. While HTLV-1 associated ALS-like syndrome has several features that may distinguish it from classical ALS, HIV-infected patients may develop neurological manifestations that resemble classical ALS although it occurs at a younger age and they may show a dramatic improvement following the initiation of antiretroviral therapy.^[32]

Virus infections as a trigger of Autoimmune Disease: Natural infections can cause exacerbations of autoimmune disease. This is most likely due to the induction of IL-12, IL-6 and IFN- γ . Previously, when nerve tissue derived rabies vaccine was used before the advent of wide usage of cell culture based vaccine post vaccination allergic encephalomyelitis was reported at a frequency of 1 in 5000 vaccines. The risk was higher when individuals received repeat cycles of post exposure prophylaxis. This had been attributed to immune response triggered to myelin basic protein, an autoimmune phenomenon. Normally the CNS is an immunologically privileged site; hence, myelin basic protein is not recognized as a self-antigen.^[33]

Another autoimmune-like disease condition is multiple sclerosis (MS) which is characterized by demyelination of nerve cells in the brain and spinal cord. Certain viruses have been linked to this process. MV was speculated to be involved and there is some evidence for linking JCV with this condition.^[34]

CONCLUSIONS

Infections of the CNS caused by viruses are of public health importance. They are acute or chronic in nature. The viruses that cause acute infection have a pathophysiology different from those that cause chronic or slow infections of the CNS. Protein infectious agents (prions) cause slow virus disease of the brain and have several unique features which distinguish them from viruses that contain genomic material which is RNA or DNA in nature. The viruses and prions reach the CNS either by breaching the BBB or traversing in the axonal sheath. Very often, several viruses have a strong viremic phase before CNS invasion. Innate and specific immunity of the host determine the establishment of the viral infection, CNS invasion and clinical outcome. Viral attributes, host immunogenetics and certain environmental factors determine the distribution and disease causation of viruses. Viral infection of the CNS could have acute or chronic morbidities which quite often result in fatality with a few exceptions. Poliomyelitis is a clinical condition with low fatality rate of all CNS infections but the sequelae of paralyzed limb(s) persist without harming cognitive function. Certain viral infections resolve with neurological

sequelae that include cognitive, motor and sensory deficits. Several unknown features exist in the understanding of the pathophysiology of CNS viral infections.

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