SUPPLEMENTAL HANDOUT

CNS complications from virus infections are rare but severe. Many viruses from different families have capacity to cause CNS disease. This lecture covers the viruses that cause CNS disease, and also focuses on the common features of CNS virulence.

Virus infection and inflammation in the CNS causes encephalitis, inflammation of the white matter (spinal cord) is myelitis, and inflammation of the meningeal layers is meningitis. There can be combinations such as encephalomyelitis. There can also be encephalopathy, i.e., brain pathology without inflammation, such as that seen in various diseases involving “infection” by unconventional agents (prions).

By the end of the lecture, you will be familiar with the most common causes of viral encephalitis, the patterns of CNS virus infections, and the concept of a prion being distinct from a virus.

Slide 2: Outline for the lecture.

1. Entry of viruses into CNS and viral pathogenesis
2. Herpes viruses
3. Entero viruses
4. Arbo viruses (specifically West Nile and Dengue)
5. Measles
6. Rabies
7. Unconventional agents (prions)
Slide 3: This slide depicts the various routes that viruses can access the CNS. The access routes include hematogenous routes to CNS, direct infection of peripheral neurons, infection of olfactory neurons (which are part of CNS), infection into the meninges from hematogenous sources.

Note that infection and disease depends on the two distinct properties of neuroinvasiveness (ability of virus to access CNS) and neurovirulence (ability of virus to cause disease once in CNS, either by directly infecting and destroying cells of CNS, and/or by stimulating pathogenic immune responses in CNS).

The hematogenous routes to neuroinvasion are seen with picornaviruses and arboviruses. The more directly neural routes are seen with herpes viruses.

Slide 4: Herpes viruses give a good example of a direct neurotropic entry route.

Slide 5: Neurotropic viruses have to be neuroinvasive. This requires that viruses enter neurons, usually at termini, then transport to cell bodies, replicate, assemble and egress. For dissemination of viruses throughout the CNS parenchyma, these processes are directional (through neural connections).

Slide 6: Herpes viruses are very common infections but only very rarely enter into the CNS. The traditional host cells for herpes viruses are epithelial cells and peripheral neurons of basal ganglia. Entry into the CNS itself is rare, but with half or more of the human population infected by herpes, the sum total of CNS encephalitis due to herpes is significant.

Slide 7: Rare CNS entry may be through olfactory neurons and then to deeper CNS regions via retrograde transport in axons.

Slide 8: The retrograde transport is from nerve endings near infected epithelia, and then to cell bodies in the ganglia. The herpes viruses can transport bidirectionally, and this property sets them apart from other neurotropic human viruses.

Slide 9: In normal herpes infections, only a very small number if ganglial cells are productively infected. Latent infection is more common. The latently infected cell harbors episomal HSV DNA. Such latently infected cells do not die. Rare virus activation (the term “activation” here refers to HSV gene expressions) will begin to make virus particles. Manufacture of HSV particles is cytolytic. The cells survive long enough to transmit viruses back to epithelium, re-seeding earlier sites of HSV
infection (note that cold sores can reappear in same sites years after original infection).

Slide 10: Widespread HSV infections in the CNS will be cytolytic in many areas, as imaged here in brain sections (note black areas). The outcome is fatal in about 40% of HSV infections. There are about 1,000 deaths per year from fatal HSV encephalitis. Intravenous, high dose acyclovir therapy is justified in HSV CNS infections.

Slide 11: HSV CNS infections will be associated with elevated leukocytes in CSF, but such elevation may not be observed in peripheral blood. Spinal taps are necessary. HSV in CSF can be identified by PCR in a circa 2h assay. Rapid detection is necessary so that appropriate antiviral therapies can be started.

Slide 12: A tough USMLE1 question.

Slide 13: Next are enteroviruses. These are viruses of the picornavirus family, small nonenveloped icosahedral plus-strand RNA viruses. They cause disease in summer months and are spread mostly among children.

Slide 14: The enteroviruses transmit by the fecal-oral route. A classic example is poliovirus. Ingested virus replicates in GALT, then spills into the lymphatic system, to the blood, and then to anterior horn cells of spinal cord. If infection of spinal cord neurons takes place, then virus can cause myelitis, paralysis, rarely encephalitis and death. Infection of neurons is rare. In most cases the virus stays in the GI tract. Vaccines against these viruses are effective because they can block the hematogenous virus from entering neurons.

Coxsackie viruses are relevant here. Novel antiviral therapies to thwart coxsackie viruses are being developed and can be used in extraordinary circumstances; i.e., in cases of childhood coxsackie virus induced encephalitis.

Slide 15: A USMLE1 question that recalls your knowledge of virus structures.

Slide 16: The arboviruses are transmitted by insect vectors. These viruses are tropical and present in the summer (think mosquitoes), affect the elderly and cause meningitis. The viruses are interesting because they have two very diverse hosts, insects and mammals.

Slide 17: The viruses are established from insect blood meals. They first infect skin DCs. They are often eliminated quickly by IFNs, if not, they are transported onward to lymph nodes, then viruses transit into blood, to generate viremia. Here they are often eliminated by antibodies or NK cells. If not, they can rarely enter CNS, infecting cells of the meningeal layers.
Slide 18: Meningitis is different than encephalitis. The cells of the meningeal layer include the pia mater, also the choroid plexus can become infected (choroid plexus can be considered an extension of the meninges). Herpes is encephalitic, while the arboviruses are (usually) meningitic.

Slide 19: WNV is the most common arbovirus in our area.

Slide 20: The WNV transmission cycle is typically from mosquito to bird and back, but rarely extends to human, or horse, or other large mammals. This transmission to humans typically breaks the virus transmission chain. That is why infection is termed “incidental” here. The virus gets in the bloodstream and then infects the meningeal layers. The disease is an immunopathology, little virus replication but extreme immune response.

Slide 21 and 22: These arboviruses are serious threats. Consider, for example the recent Zika virus outbreaks. Zika is a flavivirus, ordinarily mild, but there is good evidence that it can rarely enter the amniotic fluids, infect the fetus, cause microcephaly.

Note the seminal 2016 NEJM article.

Slide 23: Measles has been well controlled by vaccines but is reappearing somewhat in the USA. The mass vaccination efforts to eradicate measles have been in place because measles can rarely cause severe disease. Measles is an extremely contagious virus (amongst the most contagious). Disease is normally self limiting but there can be rare complications. Many of the severe measles diseases are CNS diseases. The one listed on this slide is SSPE (subacute sclerosing panencephalitis) and is uniformly fatal.

Slide 24: SSPE can be compared with two other CNS complications of measles infection. One is an autoimmune reaction in CNS, causing encephalitis. Another is progressive cytolytic replication of measles in the brain. This occurs in immunocompromised conditions (measles infection itself will be immunosuppressive). SSPE is very rare and comes from persistent replication of defective virus in the brain. These diseases justify continued vaccination against measles virus.

Slide 25: A USMLE1 question that calls upon knowledge of measles.

Slide 26: Next is rabies, an extremely rare but fatal infection from animals.

Slide 27: The virus is an enveloped minus-strand RNA virus that is bullet shaped. The virus is very prolific and after replication, viruses occupy much of the cytoplasm of infected cells (at left). All this infection is cytolytic.

Slide 28: The disease course is a morbid case of axonal viral transport to CNS, uncontrolled virus replication in neurons, dissemination of progeny virions in saliva and other secretions, then death of the host. The virus gets inoculated into muscle
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Viral Encephalitis
Tom Gallagher, Ph.D.

tissue, replicates in muscle, transmits to peripheral neurons (Ach receptor may be used by virus to get into neurons). Once in neurons, fatal outcome is very likely. Time to death is related to position of the animal bite. If in leg, then time is longer because the virus transports by fast axonal transport (several mm per day) up peripheral neurons, to CNS. In CNS, virus then transports neutrally to eye, salivary glands, where it spills out to infect others. During these processes, CNS infection is robust and host organism dies.

Slide 29: Temporal phases of rabies infection are correlated with increasingly disturbing symptoms. To my knowledge there has been at least one case of a person surviving definitive rabies infection. The vast majority of cases are fatal.

Slide 30: Suspicion of rabies infection is always taken seriously. Postexposure prophylaxis involves wound cleaning (enveloped virus is inactivated by detergents) and passive Ig transfer (anti rabies G protein antibodies directly into wound sites) and vaccination (there is a rabies virus vaccine - not given widely because the virus is so rare.......just vets and others in contact with animals get the vaccine). Rabies prophylaxis is employed more often than one might think, with considerable costs in health care.

Slide 31: Next are prions, which are not viruses but rather proteins that can generate encephalopathies.

Slide 32: The prion diseases have historical names. Kuru is the foremost of these diseases. It was discovered by Gajdusek in New Guinea. The other diseases are CJD and BSE (mad cow disease). They are rare but fatal.

Slide 33: Kuru causes paralysis and rapid death. The transmission was traced to ritual cannibalism.

Slide 34: The agent of disease transfer was very hard to accept by the scientific community. This is because it had such novel properties. Unlike viruses, the disease agent (now called a prion, for proteinaceous infectious agent), lacks nucleic acid and cannot be inactivated by chemicals and environmental conditions that kill all known viruses.

The disease is also unusual and set apart by absence of cpe and immune responses.

Slide 35: The pathology of the disease can only be identified postmortem. Brain sections reveal protein depositions (plaques) that are not unlike those seen in other protein storage disorders such as Alzheimer’s disease.

Slide 36: The concept of a prion is best understood by appreciating that proteins can exist in multiple distinct conformations. This slide depicts prion proteins extending from cell surfaces. The prion proteins are held to cells by phosphatidyl inositol. These prion proteins are found in our brains. The prion ectodomains can shed from cells. They can also adopt alternative conformations (red squiggles). The
alternative conformations can bind to the “native” conformations of the same proteins, stimulating the native conformations to convert to the alternate conformations. This is a type of protein template-induced formation of alternate (aggregated) protein conformations. Eventually, the alternate (nonfunctional) conformations accumulate. Cells may endocytose these accumulated aggregates, which in the non-pathological condition, will transit to lysosomes and be degraded. If they cannot be degraded (because they are so hopelessly aggregated and resistant to enzymatic hydrolysis), they can build up in cells, disturbing their function. This is protein storage disease, which in the CNS can have the disease complications of prion (Kuru) disease.

Slide 37: The prion hypothesis has brought some modifications to the central dogma of molecular biology, as shown here. Summarizing, (prions) are unconventional proteinaceous agents that have the capacity to seed deposition of protein aggregates, most likely through a templated reaction in which the prions catalyze refolding of endogenous proteins into their prion-like forms.

Slide 38: The USMLE1 question on slide 38 recalls knowledge on CJD prions.