



Plenary Session 5

Viral neuropathogenesis II & III

Chairpersons: H. Rübsamen-Waigmann (Wuppertal, D)
K. Yasui (Tokyo, JP)

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Molecular pathogenesis of Varicella Zoster virus infection of the nervous system

D. Gilden,¹ R. Cohrs,¹ B. Kleinschmidt-DeMasters,¹
B. Forghani,² R. Mahalingam

1. University of Colorado Health Sciences Center (Denver, USA)
2. California Dept. Health Services (Richmond, USA)

Varicella zoster virus (VZV) is an exclusively human neurotropic herpesvirus that causes approximately 4 million cases of chickenpox in the United States annually. After chickenpox, VZV becomes latent in cranial nerve, dorsal root and autonomic nervous system ganglia along the entire neuraxis. A brief overview of the physical state of VZV in latently infected ganglia will be provided. The central theme of the talk will discuss the protean array of neurological complications produced by virus reactivation. This includes zoster and zoster paresis; pre- and postherpetic neuralgia; zoster sine herpette, as well as acute, chronic and recurrent neuropathy that develop without rash; myelitis; unifocal large-vessel vasculopathy and multifocal small-vessel vasculopathy; and VZV-associated disseminated encephalomyelitis. The argument that there is no primary VZV encephalitis will be presented. Clinical features of the neurological disorders caused by VZV reactivation will be correlated with pathological and virological data. The use of PCR and antibody testing of CSF to confirm the role of VZV in producing the many varied clinical syndromes of the peripheral and central nervous system will be demonstrated, including evidence that the detection of VZV antibody in CSF even in the absence of PCR-amplifiable VZV DNA supports the diagnosis of a treatable VZV infection of the nervous system.

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Key issues in Varicella-Zoster virus latency in human Ganglia

P. Kennedy
University of Glasgow (Glasgow, UK)

Varicella-Zoster Virus (VZV) is a human herpesvirus which causes varicella (chickenpox) as a primary infection following which it becomes latent, often for decades, in trigeminal ganglia (TG) and dorsal root ganglia (DRG). VZV reactivates to cause herpes zoster (shingles) which may be followed by post-herpetic neuralgia and a variety of serious CNS complications, especially in the immunocompromised. There have been two key issues over the last decade which have dominated the neuropathogenesis of VZV latency in ganglia

(i) the identity of the cell-type in which latent VZV resides, and (ii) the nature and extent of VZV gene expression during latency.

The cell-type specificity of latent VZV was controversial for many years. While initial studies had suggested that the neuron was the site of latent virus, some subsequent reports suggested that latent VZV resided mainly in non-neuronal satellite cells. This issue was eventually resolved unambiguously using a combination of molecular techniques, including in situ PCR amplification, with the current consensus being that the neuron is the predominant site of latent VZV DNA, with only occasional satellite cells infected. The precise number of copies per cell of viral DNA is not known.

Analysis of latent VZV gene expression is important for two main reasons (i) since the functions of many of the VZV genes are known, knowledge of which viral genes are expressed will enhance understanding of the latency process, and (ii) expressed viral gene products might be used as targets for anti-viral therapy. There is selective viral gene expression during latency, with expression of VZV genes 4,21,29,62 and 63 being reported by most groups, as well as possible expression of gene 18. VZV gene 63-encoded protein has been regularly detected in TG by several groups, and there is evidence also for expression of several other VZV proteins. VZV gene 63 transcription appears to be a hallmark of VZV latency.

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Understanding morbillivirus neurovirulence

L. Cosby
The Queen's University of Belfast (Belfast, UK)

Certain members of the morbillivirus genus, canine distemper virus, phocine distemper virus and the cetacean viruses of dolphins and porpoises exhibit high levels of CNS infection in their natural hosts. CNS complications are rare for measles virus (MV) and are not associated with rinderpest virus (RPV) and peste des petits ruminants virus (PPRV) infection. However, both RPV and PPRV are neurovirulent in permissive murine strains. Human postmortem tissue, neural cell culture and animal models have been used to try and answer major questions concerning morbillivirus neurovirulence. In particular, how does the virus initially infect the brain and spread within the CNS? Which viral proteins determine neurovirulence? Why do morbilliviruses differ in the incidence of CNS complications in their natural hosts?

Studies of brain tissue from patients with the MV CNS complication subacute sclerosing panencephalitis (SSPE)

indicate that virus could enter the CNS either by direct infection of endothelial cells or in infected leucocytes, followed by infection of predominately neurones and oligodendrocytes. It has been established that MV neurovirulence in mice is partially determined by the receptor-binding, viral haemagglutinin protein. The two known MV receptors, CD46 and SLAM, have been examined in normal and SSPE brain tissue and the findings suggest that further receptors may be necessary to explain infection of the CNS with wild-type strains of MV. In both humans and mice once infection of neurones has been established, virus may spread trans-synaptically. In SSPE this is necessary, as the virus is known to acquire mutations, which prevent maturation and subsequent receptor-mediated cell entry.

It is possible that all morbilliviruses transiently infect the CNS in their natural hosts but development of disease is dependent on the efficiency of the immune response, illustrated by increased CNS involvement in immunocompromised individuals infected with MV. Alternatively, for RPV and PPRV, virus entry may be restricted due either to absence of viral receptors or failure of virus to replicate or spread in the CNS. Further studies, are required to answer these questions.

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Neuronal pathology caused by Borna disease virus

A. Hans,¹ J. Bajramovic,¹ S. Syan,¹ I. Dunia,² M. Brahic,¹
D. Gonzalez-Dunia¹

1. Institut Pasteur (Paris, FR)

2. Institut J. Monod (Paris, FR)

Borna disease virus (BDV), a non-segmented, negative stranded RNA virus, persists in the central nervous system (CNS) of a wide range of animal species and causes behavioural abnormalities and diverse pathologies. There is considerable evidence that BDV infects humans and infection has been claimed to be associated with certain neuropsychiatric disorders. The possible implication of BDV in human health provides further impetus for elucidating the consequences of BDV persistence in the CNS. Studies on animal models have shown that BDV infection can be associated with neuronal dysfunction and neurodevelopmental abnormalities without immunopathology. Since the replication of BDV is non cytolytic, the mechanisms underlying BDV neurotoxicity are not well understood. One hypothesis is that infection with BDV may modify the response of the infected neurons to neurotrophic factors. Neurotrophins are instrumental in regulating neuronal survival and process outgrowth in the CNS. We have developed neuronal culture systems to better examine the impact of BDV infection on neuronal physiology. Such a system is very valuable to study the factors involved in BDV infection and spread within neuronal networks, as well as the consequences of BDV persistence in neurons. In particular, we have observed that infection of neurons with BDV, although not causing overt structural defects, blocks neurotrophin responsiveness of the infected neurons and alters neuroplasticity. Infection interferes not only with early responses to neurotrophins, such as the phosphorylation of MAP kinases, but also with synaptic remodeling processes accompanying long-term exposure to neurotrophins. These findings may be of importance to explain the bases for BDV-induced cognitive and neurodevelopmental alterations.