Viral Infections and the Pathogenesis of Multiple Sclerosis

Micheline McCarthy, MD, PhD
Bruce Carter Veterans Affairs Medical Center
Miller School of Medicine, University of Miami
Miami, FL
MS: a disease with demyelination, axonal injury, white matter (and gray matter?) degeneration

Epidemiology and pathogenesis of MS: Is MS a rare complication of a common microbe (e.g. virus)?

If viruses are an environmental risk factor for MS, how can viruses contribute to pathogenesis of MS?
Pathogenetic Features of MS
What viral infections share these features?

- Inflammatory lesions in CNS
- Genetic susceptibility can occur
- Preponderance of CD8+ lymphocytes
- CSF Oligoclonal Bands
- Axonal Loss
- Gliopathy - Astrocyte and oligodendrocyte injury and death
<table>
<thead>
<tr>
<th>Virus</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabies</td>
<td>1946</td>
</tr>
<tr>
<td>Herpes Simplex type 2</td>
<td>1964</td>
</tr>
<tr>
<td>Scrapie-like agent</td>
<td>1965</td>
</tr>
<tr>
<td>Measles</td>
<td>1972</td>
</tr>
<tr>
<td>Parainfluenza virus 1</td>
<td>1972</td>
</tr>
<tr>
<td>SV5</td>
<td>1972</td>
</tr>
<tr>
<td>Simian cytomegalovirus</td>
<td>1978</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>1979</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>1980</td>
</tr>
<tr>
<td>Herpes Simplex type 1</td>
<td>1986</td>
</tr>
<tr>
<td>HERV</td>
<td>1989</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>1994/1995</td>
</tr>
<tr>
<td></td>
<td>2000</td>
</tr>
</tbody>
</table>
Potential Links between Viral Infection and the Pathogenesis of MS

- A variety of viruses may precipitate clinical MS attacks
- Epidemiology of MS: environmental exposure in childhood in genetically susceptible individuals
- Viral infection may be a co-factor interacting with the immune system
  - immune stimulation from viral antigens and viral infection
  - may be associated with persistent or re-activated viral infection
Potential Links between Viral Infection and the Pathogenesis of MS

- Virus may cause cytopathic effect directly on oligodendrocyte (example – HHV-6 infection)

- Virus may elicit cytotoxic immune response against virally-infected oligodendrocyte
Antibodies to Viruses:  
Is there a different pattern among MS patients that implies a role for viruses?

- Increased serum titers may occur:
  - measles, parainfluenza 3, influenza C, varicella, HSV, EBV (capsid, nuclear antigen), rubella (E2 glycoprotein), HTLV-1, HHV-6 (IgM)

- Differentially elevated anti-viral antibody responses
  - Increased titers to Rubella E2 but not E1 glycoprotein
Viral Infection as Immunological “Trigger” in MS

- Activation of cellular immune responses in response to acute viral infection
- Stimulation of antigen-specific immune responses and programming of memory T-cells
  - Role of molecular mimicry and epitope spread
Theory of Molecular Mimicry

- Viral Ag with similar peptide sequence to a myelin Ag
- Stimulation of T cells specific for viral Ag
- Cross reaction with normal myelin Ag
- Local inflammatory and demyelinating reaction
Theory of Epitope Spread

- T cells specific for a single Ag (myelin or viral)
- Local inflammation and demyelination
- Activation of T cells specific for other myelin Ags
- Progressive inflammation and demyelination
Viral Infection as Immunological “Trigger” in MS

- Response to viral infection fails to “shut down”
- Failure of adequate suppressor T-cell activity
  - Deficiency of suppressor-inducer T-cell subsets?
  - Viral infections (e.g. HIV-1) that can affect these subsets
Potential Links between Viral Infection and the Pathogenesis of MS

- Viral infection may cause oligodendrogliopathy
  - Oligodendrocyte injury as the “first event”
  - Example: Papovavirus causes cytopathic infection of astrocytes and oligodendrocytes
Potential Links between Viral Infection and the Pathogenesis of MS

Abnormalities of the immune system may cause re-activation of latent viruses
Human Herpesvirus-6 & MS

- **Lymphotrophic beta herpesvirus (like CMV)**
  - replicates productively in activated CD4+ T-cells, neural cells, endothelial cells, fibroblasts
  - May be capable of establishing a latent state
  - May invade the CNS directly

- **Associated with childhood illness:**
  - Roseola (exanthum subitum)
  - Febrile convulsions

- **Cause of meningoencephalitis**
  - transplant patients, other immunosuppressed
  - immune suppression alters virus infectivity and host susceptibility
Human Herpesvirus-6

- Virus infects oligodendrocytes and astrocytes

Herpesvirus-6 infection of human astrocytes in cell culture
“Direct” Evidence for HHV-6 Infection

Viral DNA or RNA sequences

- HHV-6 viral DNA in MS patient brains, including viral DNA in MS plaques
- HHV-6 viral DNA reported in patients’ sera and PBMC
- Is HHV-6 a “natural component” of CNS flora?
Anti-viral Antibodies

Antibody Titers and HHV-6:

- Increased serum IgM but not IgG response to HHV-6 early antigen (p41/38) in RRMS compared to CPMS, OND, OID, controls
- Reflects viral persistence?
- Few studies detect viral antibody in CSF
Human Herpesvirus-6 & MS

- Herpesviruses are associated with ubiquitous latent infections and frequent re-activations

- Does HHV-6 “active” infection in MS represent a symptom rather than a cause of MS?
  - MS could cause re-activation of HHV-6 from latent childhood infection

- Aggregate of HHV-6 studies not conclusive or consistent, but suggest a potential role for active HHV-6 in MS patients
Epstein-Barr Virus & MS

- Herpesvirus associated with B-lymphotrophic infection
- Infection of B-cells: can produce lytic infection or latency
- Potential for re-activation
  - Example: recurrent tonsillitis linked to recurrent EBV
- Infection in adolescence or adulthood: infectious mononucleosis (IM)
Epstein-Barr Virus & MS

- Prior history of IM is risk factor for MS
  - Relative Risk (RR) 2.17
    - Meta-analysis of case control and cohort studies
    - EBV variant of hygiene hypothesis
- Prior history of IM increases risk of MS associated with HLA-DRB1
  - DRB1 and IM → 10-fold higher risk
- Risk of MS associates with higher anti-EBNA antibodies
- CIS patients also show higher anti-EBNA IgG
Epstein-Barr Virus & MS

- EBV DNA in plasma detected in MS patients before onset (RR 2.5) – Nurses’ Health Study
- No association between quantitative EBV DNA load and MS risk
- MS patients have decreased CD8 T-cell responses to EBV-infected cells.
  - Studies using EBV-infected B-cell lymphoblastoid cell lines to measure T-cell responses
  - Decreased CD8 T-cell response could lead to accumulation of auto-reactive EBV-infected B-cells
Evidence: EBV infection and MS Risk

- Latitudinal gradient
- IM
- EBV serum Abs
- EBV DNA in CNS
- EBV specific T-cell responses

1. EBV-specific T-cells or antibodies cross react with myelin antigens (molecular mimicry)

2. Latent EBV antigens in infected B-cells promote the survival of myelin-specific B-cells

Does EBV initiate or perpetuate the MS disease process?
3. EBV could stimulate other latent viruses (HERV)
4. Activation of myelin-specific B cells promotes EBV replication and EBV-specific T- and B-cell responses (EBV is an epiphenomenon)

Is EBV an epiphenomenon of a causative immune derangement?
Viruses and Pathogenesis of MS: Some Animal Models

- **Theiler’s virus** (*Picornaviridae*) of mice: associated genetic susceptibility of some strains of mice; persistent, restricted (non-productive) oligodendrocyte infection

- **Mouse Hepatitis Virus** (*Coronaviridae*): Viral strains vary in neurovirulence (viral glycoprotein S), genetic differences in antibody and cellular immune responses

- **Semliki Forest Virus** (*Togaviridae*): neuroinvasive and neurotropic virus; changes in blood-brain barrier, virus infects neurons and oligodendrocytes, secondary demyelinating immune response
Obtaining CME Credit

• If you would like to receive CME credit for this activity, please visit:

http://www.pesgce.com/PVAsummit2011/

• This information can also be found in the Summit 2011 Program on page 8.