Invited Minireview

Multiple Sclerosis and Measles Virus

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SUMMARY: Epidemiological studies suggest that patients with multiple sclerosis (MS) are exposed to some infectious agent(s) before puberty. The presence of virus-induced demyelination in animal models indicates that demyelination can occur following the trigger of a virus infection. Data regarding the immunological abnormalities to measles virus (MV) and the presence of neurological complications induced by MV infection suggest that MV may be a causative agent of the demyelination observed in MS. Numerous virological studies (e.g., morphological observation, virus isolation, and the search for the MV gene) have been performed, though definite evidence identifying MV as the causative agent has not yet been obtained.

1. Introduction

Multiple sclerosis (MS) is a representative human demyelinating disease. The disorder occurs most frequently in young adults, generally with periodic exacerbations and remissions. The intervals of exacerbation and remission are indefinite, however, the course of the disease is generally progressive. Demyelination and sclerotic lesions at more than two distinct sites in the white matter characterize the neuropathological findings of MS (Figure). The first case of MS was reported by Charles Prosper Ollivier in 1824, and Charcot described the clinical features of MS as a discrete and diagnosable entity in 1868 (1).

The exact pathomechanisms of MS have not been fully clarified, however, accumulated data suggest that immunological abnormalities play an important role in susceptibility to MS. Epidemiological studies have indicated that infectious agents play a role in inducing these immunological abnormalities. Here, I review the reasons why measles virus (MV) is suspected to be a causative agent of MS, and is thought to be involved in its pathogenesis.

2. Data from experimental animal models indicate the presence of virus-induced demyelination

One reason that many investigators believe infectious agent(s) are involved in the pathogenesis of MS is that there are several animal models of virus-induced demyelination in the central nervous system (CNS) (Table). In these animal models, pathological features of demyelination with inflammatory cell infiltration are reminiscent of those found in MS. Among these models, the demyelinating disease induced by Theiler's murine encephalomyelitis virus (TMEV) infection in the spinal cords of mice has been extensively studied (2, 3). In the late 1980s, the entire nucleotide and predicted amino acid sequences were determined, and full-length infectious cDNAs were constructed. These studies provided the opportunities for molecular genetic studies to elucidate of TMEV-induced demyelination. Data from the animal models demonstrate that viruses can cause demyelination in their hosts either directly and/or indirectly. In those animal models, both viral genomic and host factors are considered to influence demyelination since some strains of virus are more likely to result in demyelination and some mouse strains have been shown to be more sensitive to demyelination than others. The data obtained from these animal models are valuable to an understanding of the mechanisms of demyelination in MS.

Table. Experimental animal models of virus-induced demyelination

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virus group</th>
<th>Natural host</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theiler's murine encephalomyelitis virus</td>
<td>Picornavirus</td>
<td>Mice</td>
</tr>
<tr>
<td>Canine distemper virus</td>
<td>Paramyxovirus</td>
<td>Dogs</td>
</tr>
<tr>
<td>JHM strain of mouse hepatitis virus</td>
<td>Coronavirus</td>
<td>Mice, Rats</td>
</tr>
<tr>
<td>Visna virus</td>
<td>Retrovirus</td>
<td>Sheep</td>
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</table>

3. Epidemiological data suggest an infectious agent is involved in the pathogenesis of multiple sclerosis

Epidemiological data over the past 50 years strongly indicate that MS is related to environmental exposure in childhood.
The geographical distribution of MS patients is very specific. Generally, MS increases in frequency with latitude in both the northern and southern hemispheres. At the equator, MS is rare, while the incidence of MS in the northern United States, southern Canada, Northern Europe is 30-80 cases per 100,000, decreasing to 6-20 cases per 100,000 in most of Southern Europe and the southern United States. The number is even lower, with rates of 1-4 cases per 100,000, in Asia, Africa, and on the Caribbean coasts. In South Africa, the prevalence rate of MS among immigrants who were born in North Europe was found to be 49 per 100,000 in comparison with a prevalence of 11 per 100,000 among native-born English-speaking white South Africans (4). The risk of developing MS was reduced to less than one third of that expected risk among those who immigrated under the age of 15 or 16. This suggests that exposure before puberty to some environmental factor(s), possibly an infectious agent, could play an important role in the pathogenesis of MS. However, data on immigrants moving from low- to high-risk areas are less complete (5).

4. Post-measles encephalomyelitis

The presence of post-MV infection neurological complications, including a demyelinating disease, suggests a possible relationship between MV and MS. These neurological complications are divided into three distinct categories: measles inclusion-body encephalitis, subacute sclerosing panencephalitis (SSPE), and postinfectious encephalomyelitis (PIE) (6). The neuropathological findings seen in PIE include perivascular inflammation and demyelination. The pathologic findings resembling those seen in experimental allergic encephalomyelitis suggest that PIE is an autoimmune (hypersensitive) disease (7, 8). Interestingly, the virus has rarely been recovered from the brain in PIE (6). Therefore, MV is considered to be able to induce demyelination without invading the CNS.

5. Multiple sclerosis and measles virus

1) Serological studies

Based on the above-described data, Adams and Imagawa tested the hypothesis that MV might act as a causative agent for MS, and carried out serological studies on complement-fixing and neutralization antibody titers to MV in the sera of MS patients (9). They found that 36% and 31% of MS sera showed significantly high titers in MV neutralization and complement-fixation tests, respectively. In contrast, only 14% and 12% of control sera were positive for these respective tests. In addition, over 75% of MS cerebrospinal fluid (CSF) showed positive neutralization titers while no control CSF showed a positive titer. After this report, a number of studies examining antibody titers to various viruses in MS were carried out. Although over 70% of MS CSF showed positive antibody titers against MV, MS CSF demonstrated positive antibody titers to other viruses as well (10). These results suggest that CSF antibody titers are not specific to MV. Of note, high serum antibodies to MV have been found in disorders other than MS, such as lupus erythematosus, Reiter’s syndrome, and chronic liver disease (11).

The presence of oligoclonal bands (oligoclonally distributed IgG) in the CSF is a characteristic feature of MS. Oligoclonal bands in the CSF result from the expansion of several clones of B-cells, and consist of immunoglobulin which is directed to single, specific, or several discrete antigens in the CNS. MV-specific IgG in the CSF of MS patients is less than 5% of the total IgG, whereas it is 30-60% of the total in CSF of patients with SSPE (12). In addition, oligoclonal bands in SSPE can be absorbed out with MV preparations although those in MS cannot.

2) Morphological studies

Several investigators have found measles virus-like or paramyxovirus-like structures by electron microscopy in autopsied MS brains (13-15); these include intranuclear and cytoplasmic tubular structures, intranuclear dense strands, cytoplasmic membrane-bound twisted tubules, etc. However, such structures have not been positively stained by immunoelectron microscopy using an antibody specific for MV (15). In addition, such structures have been reported in other neurological diseases such as Guillain-Barré syndrome, herpetic encephalitis, lipidosis, etc. (15).

3) Virus isolations

There are a variety of reports regarding virus isolation from MS brains. However, the number of reports of MV isolation from MS brains is limited. Field et al. reported that explants of an MS patient’s brain developed cytopathic changes in LLC-MK2 cells, which were neutralized by rabbit anti-MV serum (16). However, the authors allowed the possibility of laboratory contamination. As noted above, MV can induce hyperergic encephalitis without invading the CNS. The findings prompted a search for the presence of MV outside the CNS. Pertschuk et al. reported that MV antigen was identified by immuno-fluorescence in epithelial and lamina-propria cells of the jejunum of 24 MS patients, but in none of 20 controls (17). In addition, MV was recovered by cocultivation or cell-fusion techniques from jejunal biopsy specimens from 6 MS patients (18). Although these findings were partly confirmed in some Japanese MS patients (19), attempts by other laboratories to confirm these results failed (20, 21).

4) Search for measles virus genes

By an in situ hybridization technique, MV-specific RNA has been found in two foci in one of four cases of MS (22). Cosby et al. detected the MV nucleocapsid protein gene in two of eight MS cases, but they also found it in one control (23). Interestingly, Katayama et al. detected a portion of the MV mRNA encoding nucleoprotein (NP) sequence in 11 of 61 brain tissue samples obtained from administrative autopsy cases, who apparently had not suffered from SSPE (24). These data suggest that MV can persist in human brains without relating to MS. Other studies have failed to detect any MV genes in MS brains (25, 26).

6. Future prospects

The recent identification of the human MV receptor, CD46, and the subsequent generation of a transgenic mouse model have provided a new system for the study of MV CNS infections (27, 28). Studies of this model have demonstrated that MV suppresses humoral and cellular immune responses. In addition, MV was found to replicate primarily in neurons, then spread to distal sites by axonal transport. Although demyelination has not yet been reported, further studies may clarify the relationship between MV and demyelinating disease.

7. Conclusions

Epidemiological studies suggest that patients with MS are exposed to an infectious agent(s) before puberty. MV infections produce immunological abnormalities and demyelinating disease, raising the possibility that MV may act as a causative
agent of MS. In spite of numerous virological studies, no definite evidence has yet identified MV as the causative agent of MS. However, the failure to isolate or detect MV in MS patients does not completely rule out a relationship between MV and MS.

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