Infection and the Etiology and Pathogenesis of Multiple Sclerosis

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Multiple sclerosis (MS) currently defies clinical and scientific definitions, and carries a prognosis that remains practically unchanged despite many years of intensive research. Although the prevailing dogma is that MS is an immune-mediated condition, it fulfills none of the criteria of an autoimmune disease. On the other hand, there is enough significant data to suggest that infectious agents(s) could be involved in either direct damage to the white matter or induce inflammatory responses that secondarily affect the brain. Our goal here is to review the data supporting the possibility that infection has a critical role in the disease, examine the list of potential candidates that have been suggested, and outline an approach regarding the potential role of infectious agents in the etiology and pathogenesis of MS.

Introduction

Despite years of investigation, no direct evidence has been found to incriminate a specific etiology and pathogenesis for multiple sclerosis (MS). Based on meager evidence [1•] and on extrapolation, an autoimmune pathogenesis has been hypothesized. However, we feel that autoimmune pathogenesis is not the likely culprit; instead, we believe that infection is more likely responsible for the damage to the central nervous system (CNS). We review the data for an infectious process and examine the list of potential candidates.

Multiple sclerosis is a chronic, inflammatory white matter disease of the CNS that usually affects young adults. Successive sets of diagnostic criteria, essentially requiring objective evidence of at least two distinct lesions of CNS white matter (the last set almost 20 years old), allude not only to the absence of a pathognomonic test for MS, but also to the lack of adequate evidence for the reliability of the various criteria. Of note is the requirement for lack of an alternative diagnosis [2], a criterion that imposes an element of "diagnosis by exclusion." The white matter is progressively destroyed, leaving some of the victims incapacitated for life. For many years, the leading, and practically dogmatic, hypothesis has been that MS is an autoimmune condition and hence, that its symptoms and progression could be ameliorated by immunomodulating strategies. However, while the field of neuroimmunology has thrived, little progress has been made towards understanding MS. The current diagnostic criteria accommodate a wide range of conditions. Indeed, the extremely variable course and prognosis of the disease suggest that what is considered today a homogenous and consistent entity of similar etiology and pathogenesis, is, in fact, a syndrome caused by various etiologies and multiple pathogenic mechanisms [1•].

Pierre Marie, Charcot's favorite student, (but not his successor, as erroneously suggested by several reviews), was the first, at the end of the 19th century, to raise the possibility that MS is caused by an infection [3]. Since then, the amount of information in this realm is overwhelming. Our goal here is not to quote the copious literature, but to delineate concepts, outline an approach, and provide some food for thought regarding the possible role of infectious agents in the etiology and pathogenesis MS.

Circumstantial Evidence

Basically, an infective process can damage the tissue via two major avenues: directly, due to the pathogen present in the tissue during the disease; or indirectly, where the infection is only the trigger, and the damage occurs while the infection has already been cleared and removed from the organism. Each alternative has different histologic, serologic, and epidemiologic characteristics.

Direct infection

Pathology

Multiple sclerosis lesions (plaques) are multifocal and mainly perivenous [4••]. Their distribution, though random enough to merit conflicting generalizations and conclusions, can reflect the route of penetration of infection. The myelin loss, with neurons and axons being relatively spared, which is characteristic of the MS lesion, is associated with mononuclear inflammatory cell infiltrates within active plaques and in perivascular spaces. Macrophages and T lymphocytes are present in the center of a new lesion, which also shows reduction in the number of oligodendrocytes, reactive astrocytes, and microglial cells. Obviously, these findings may accompany an active ongoing infectious process. The predilection of the inflammation for the white matter is a

relatively uncommon feature of acute viral infections of the CNS, and has been noted mainly in certain chronic viral infections (see following).

Epidemiology

This discipline has provided compelling evidence for an environmental factor in MS. For example, disease distribution in different geographic regions can be classified according to climate [5•]. Although differences in quality of healthcare systems and recording in different countries may temper this finding, it seems that there is a high prevalence (or risk) in temperate countries (northern Europe, United States, Canada, southern Australia, and New Zealand), a low prevalence in warm, equatorial regions (the Caribbean, Mexico) and a medium prevalence in between (southern Europe).

Migration might also induce epidemics. Probably the best-studied example is the outbreak of an MS epidemic in the Faroe Islands following stationing of British troops there during the Second World War [6]. Migration studies have also suggested that age at the time of migration is important. In many instances, when individuals migrate prior to 15 years of age, they exhibit the prevalence of their new home. If they migrate at a later age, they retain the disease prevalence of their native country. This has been used to argue for the presence of an infectious factor, because there are examples for the critical role of the timing of primary infection in induction of an infectious CNS disorder [7].

Conjugal and cluster multiple sclerosis

Anecdotal evidence of occurrence of MS in families has been noted for many years [8]. There are few reports of conjugal MS [9] and of MS diagnosed in children of affected parents [10], but not enough to enable statistical analysis. Whether these reports, together with other documentation of MS affecting members of the same community [11], those who share a profession, a work place, or a residence are more than just coincidental anecdotes is not settled.

Experimental models

With no true understanding of the cause of MS, the animal demyelinating disease models abound. There is quite a spectrum of viruses that can produce acute and chronic demyelinating conditions in a variety of experimental animals [12]. These include DNA viruses such as the papova virus SV40 (rhesus monkeys) and herpes simplex virus type 1 (HSV-1) and 2 (in mice), RNA viruses such as canine distemper virus (mice and hamsters), several corona virus models in mice and monkeys, the murine picorna Theiler's virus, and retroviruses such as visna virus in sheep. These models prove the concept that viruses can induce demyelination.

Interferons for the treatment of multiple sclerosis

As of today, three β-interferon preparations are licensed for the treatment of MS. They were shown to have a moderate effect upon disease relapse rate and progression of disability [13–15]. Interferons are naturally occurring species-specific glycoproteins that were first discovered in 1957 because of their antiviral activity, but they also possess a variety of other biologic actions. They belong to the ever-growing group of cytokines that are capable of modulating the immune system. Nevertheless, one of their major functions is to combat viral infections. They are in clinical use for treatment of conditions such as infections due to hepatitis B and C viruses, and genital warts caused by papillomavirus. Although it has been argued that the β-interferons' effect upon MS is immunomodulatory, the possibility that their impact is directly antiviral is just as likely.

Infective human demyelinating disorders

Viruses can cause a variety of naturally occurring human CNS demyelinating diseases. Infective and postinfective conditions have been noted: progressive multifocal leukoencephalopathy (PML) and tropical spastic paraparesis are examples of the first, whereas postinfectious encephalomyelitis occurs following diverse infections. Although these disorders are clinically distinct from MS, they nevertheless suggest that viruses are capable of inducing demyelinating diseases in the human CNS.

Cerebrospinal fluid

Cerebrospinal fluid (CSF) oligoclonal bands are present in the vast majority of MS patients. Although attributed to a chronic immune-mediated process, CSF oligoclonal bands are also a feature of chronic CNS infections [16].

Multiple sclerosis as a postinfective condition

In view of the current dogma of MS as an immune-mediated disorder, the possibility that the disease and/or its relapses are triggered by infections, whereas the eventual tissue damage is due to immune activation, might be more appealing than the concept that MS is a true infective process. The methodology used to examine an association between infection and clinical diseases is both epidemiologic and serologic/immunologic.

Epidemiology

Some studies that examined the association between antecedent infection and occurrence of MS may suggest a sequential relationship. These included unspecified infections [17] and infections with specific agents, such as measles [18] and Epstein-Barr virus (EBV) [19].

There seems also to be a relationship between an infection and the occurrence of a relapse in a setup of already defined clinical MS [20]. Approximately 9% of infections were temporally related to exacerbations, whereas 27% of exacerbations followed infections. This observation was confirmed by a prospective study that followed MS relapses by magnetic resonance imaging (MRI) [21]. MS relapses also tended to have a seasonal increase, in association with respiratory infections.

Immunology/serology

Immunology/serology can serve to suggest both an ongoing infectious process and/or a previous exposure to a pathogen. Antiviral antibodies were examined in the serum and the CSF of MS patients. Higher titers of antibodies against a large spectrum of viruses were found (but not always confirmed) in MS patients when compared with control patients. The list [12,22] includes measles, parainfluenza, influenza, varicella zoster, HSV, rubella, EBV, mumps, human T-cell lymphotropic virus (HTLV)-1 and 2, and several others.

Direct Evidence

Direct proof that a pathogen is responsible for the tissue damage in MS requires isolating the agent from the diseased nervous system and demonstrating that this finding is disease-specific. So far, this task has eluded researchers: no virus or any other infective agent has met these criteria. Isolating a pathogen from MS patients' tissues is based on the available technology. For more than half a century, a wide spectrum of laboratory approaches has been used, from cytopathic effect produced in culture by fluids isolated from patients, to viral culture and cocultivation studies, to the present polymerase chain reaction (PCR) amplification and representational difference analysis.

A long list of suspected viruses includes rabies, HSV, scrapie agent, parainfluenza, measles, simian virus V, coronavirus, HTLV-1, and others. None has withstood tests of reproducibility, specific presence in a significant number of MS patients as compared with control patients, or a reasonable experimental explanation. Nevertheless, based on the assumption that we are dealing with a heterogeneous entity, most likely a syndrome, it is possible that the disorder is due to many different pathogens, where in certain individual cases, an isolated pathogen is indeed responsible for the disease. Therefore, several or all such pathogens might cause the disease, but would not stand out when examined on a large series of patients.

As of today, four pathogens are under scrutiny, and are, therefore, discussed here in more depth.

Human herpes virus 6

Human herpes virus 6 (HHV-6) is a lately discovered DNA virus that is responsible for exanthema subitum (roseola infantum) in children; up to 95% of the general population has been exposed to it [23]. It is a lymphotropic and a neurotropic virus that has been shown to infect glial cells in culture [24]. A look at control tissues, PCR amplification of HHV-6 nucleic acids, and representational difference analysis (the technology that enabled to link HHV-8 with Kaposi's sarcoma) demonstrates that it resides in the nervous system of the majority of the population [25]. HHV-6 has been linked with a variety of acute and chronic neurologic disorders, such as encephalitis [26], meningoencephalitis [27], and myelopathy [28] under normal or immune-compromised states.

A possible association between HHV-6 and MS is suggested by a number of studies. These include studies that find higher levels of anti–HHV-6 antibodies in the sera of patients with MS as compared with control patients [29,30•], studies that identify HHV-6 DNA in a larger percentage of MS patients compared with control patients [30•] (findings which are not confirmed by other groups [31]), and evidence for HHV-6 gene expression in the brain, in oligodendrocytes, and in plaques of MS patients [25,32•]. The latter findings, however, were not confirmed by other researchers [33].

Although not unique to HHV-6, it is important to note that the timing of exposure to the virus corresponds with the exposure time to a possible infectious pathogen in MS. At present, the most intriguing finding is the association of HHV-6 with MS lesions. If confirmed, it should lead to the question whether this is an outcome of the disease (or its treatment, as the immunosuppressive and immunomodulatory therapies may induce viral reactivation with expression of viral gene products), a noncontributory factor, or indeed related to the pathogenesis of the disease.

Epstein-Barr virus

Epstein-Barr virus is a lymphotrophic herpes virus responsible for infectious mononucleosis that has been associated with a spectrum of neurologic disorders, including certain CNS lymphomas. Like other herpes viruses, it establishes latent infection and can reactivate later [34]. In several studies, EBV was found to be present or have left evidence of previous exposure in a higher percentage of MS patients compared with control patients [35]. Likewise, epidemiologic studies suggest a relationship between a previous EBV infection and MS [19]. It is worth noting that, during acute EBV infections, antibodies that cross-react with neuroglial antigens are produced [36].

However, identification of the pathogen(s) in MS cannot rely on fingerprints alone. It is mandatory to detect presence of viral nucleic acids and/or antigens in the diseased tissue, which should not constitute a technical problem because EBV is already revealed and examined in certain CNS lymphomas. We are not aware of any report on the presence or absence of such compounds in brain tissues of MS patients.

Retroviruses

Retroviruses are RNA viruses that encode proviral DNA integrated into the host cell genome and can be transmitted via the germ line [37]. Endogenous retroviral sequences constitute up to 20% of the human genome. The retrovirus visna, found in sheep, was one of the first animal models of a demyelinating disease, and HTLV-1, which can cause a human demyelinating chronic myelopathy, was implicated, but not confirmed, as the cause of MS.

In the past decade, another, yet unidentified, retrovirus has been traced. Activity of the retroviral enzyme reverse transcriptase was identified in tissues and cells from MS patients [38•], as well as retroviral sequences in the CSF [38•] and serum [39]. This has come to be termed MS-associated retrovirus (MSRV). Indeed, endogenous retrovirus can theoretically induce an immune-mediated condition [40] or an infectious process per se. Unfortunately, other groups were unable to confirm these findings, and there is a similarity between the identified sequences and those of endogenous retroviruses present in the majority of the population [38•].

A collaboration between a retrovirus and EBV in inducing MS and triggering the relapses has also been suggested [41•]. The hypothesis is based on the observation that herpes viruses can transactivate retroviruses [42], and on the ability of herpes viruses to reactivate periodically and induce recurrent disease [34].

Chlamydia pneumoniae

Chlamydia pneumoniae is an obligate, intracellular, gram-negative bacterium known to cause respiratory infections in humans. The organism has also been implicated in a wide variety of disorders ranging from asthma, atherosclerotic vascular disease, and arthritis to Guillain-Barre syndrome and encephalitis. The possible relation of *Chlamydia* to MS was recently resurrected by a case report of a 24-year-old man who presented with a fulminant MS-like disease [43]. His condition deteriorated despite corticosteroid and β-interferon therapy. Although treated with cyclophosphamide, CSF cultures and PCR analysis turned out to be positive for *Chlamydia pneumoniae*, and prolonged antibiotic therapy was associated with neurologic recovery. This report was followed by analysis of 37 additional patients from the same center [44••], showing 64% of CSF samples culture-positive, and 97% PCR-positive for the organism, (compared with 11% and 18% in control patients, respectively), and 86% with CSF anti-*Chlamydia* antibodies. These findings were supported by one group [45], but not by others [46]. Although the discrepancies may be due to lack of uniform standards and technical difficulties, it seems remarkable that a bacterium with distinct morphologic features could have eluded generations of neuropathologists. Furthermore, recent studies failed to detect *Chlamydia* DNA within brain lesions obtained by biopsy or autopsy of MS patients [47]. Thus, although in some geographical areas some MS patients may have a chronic CNS *chlamydial* infection, its cause and effect role in MS is questionable, because the pathogen is known to infect macrophages and could secondarily gain entrance into the CNS during MS exacerbations [44••].

Mechanism of virus-induced demyelination

Many details concerning the mechanism of myelin damage in MS are still obscure, but putative models for activated T-cell penetration of the CNS with resultant demyelination have been put forward [48]. Thus, injury might be due to a concerted effect of cytokine- and antibody-mediated injury, direct injury to oligodendrocytes by CD4+ and CD8+ T cells, and myelin digestion by macrophages. Naturally, a heavy emphasis on the immune response to self-antigens is the premise of these models, but such cascades could still be easily compatible with the presence of microbial agents as the primary inciting events, or as modulatory factors during ongoing inflammation. After 50 years, no breakthrough evidence to support either a pure autoimmune pathogenesis or a direct destructive infection of white matter components has become available.

Infection could take part in tissue damage via a direct, PML-like infective process. Although it might be argued that the attempts to treat MS with intense immunosuppression should have induced exacerbations attributed to enhanced viral proliferation (which they usually did not), there are certain nervous system persistent or latent infections that are not influenced by the host's immune state [34].

At the other end, any intercurrent infection may induce an antimyelin immune response through molecular mimicry (*ie*, microorganism antigens that resemble myelin antigens that are presented to the immune system under conditions which favor breakdown of self tolerance followed by the myelin being attacked by the newly primed effector cells and autoantibodies) [49]. Indeed, microbial epitopes resembling myelin basic protein have been shown to induce experimental autoimmune encephalomyelitis [50••], and fine specificities of altered epitopes capable of inhibiting the self response are under study. However, Guillain-Barre syndrome and paraneoplastic disorders in which molecular mimicry is thought to play a central role are either mainly monophasic or subacute progressive disorders, not characterized by frequent relapses. Additionally, some viruses may act as superantigens [40] that bind outside the antigen grove, and activate whole classes of T cells, including autoreactive T cells specific for myelin antigen(s), which once activated may cross the blood-brain barrier.

There are also possibilities that combine these two extremes. Theoretically, latent viral infection of oligodendrocytes (capable of frequent mutations) may occasionally express novel gene products that will be recognized as foreign, and the immune system will eventually mount an inflammatory response with extensive local damage. The relative immune privilege of the CNS may support such damage, because single cells harboring the virus will remain undetected and the immune response delayed, enabling tissue alteration to spread locally, causing a more extensive response later. Other possibilities are even more hypothetical. For instance, double infections, in which products of one infectious process enhance a nonspecific or specific responses to a second or a latent pathogen, might be also considered.

The answers are probably more complex and multifactorial. The infection could be the primary etiology, but

an immune-mediated response will play an important pathogenic role. Alternatively, if MS is indeed a syndrome, inter-patient differences may account for the difficulty in establishing a unifying hypothesis on MS etiology. This is supported by a recent pathologic study [4••], where four different demyelination patterns, two showing evidence for a viral- or toxin-mediated oligodendrocytopathy, are suggested. At any rate, non-unifying approaches aimed at splitting the syndrome of MS into distinct entities are probably necessary to unravel the mystery of MS etiology.

Conclusions

We have provided the data in favor of an infectious etiology of MS. However, as of today, there is still no evidence to incriminate a specific pathogen. The hunt is still on, and until the causative agent and the destructive scheme are be exposed, the neurologic scientific and clinical community will not give up.

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