Is multiple sclerosis CNS leprosy?

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Abstract

Multiple sclerosis (MS) is widely believed to be an autoimmune disorder. Another exciting idea regarding the aetiology of MS may be that the immune response in MS could result from a chronic infection rather than autoimmunity in the usual sense. M. leprae-induced myelin damage in the early infectious process provides valuable insights into the pathologic mechanisms of multiple sclerosis. However, no research has hypothesized the possible involvement of mycobacterium leprae or its components in pathogenesis of MS. Most of the antigens of mycobacterium leprae and mycobacterium tuberculosis are members of stress protein families. Of the M. leprae and M. tuberculosis antigens identified by monoclonal antibodies, all except the 18-kDa M. leprae antigen and the 19-kDa M. tuberculosis antigen are strongly coded with very similar genes. I hypothesize that MS is a syndrome of diseases, induced by intradermal BCG vaccine which may contain the antigen component resembling that of leprae that can either produce central demyelination by itself, or by delayed hypersensitivity. The hypothesis should be assessed in several experimental and clinical trials. If my hypothesis can be verified experimentally and clinically, then measurements to prevent MS disease could be accomplished.

Keywords
Multiple sclerosis, Mycobacterium leprae, BCG

Introduction

Multiple sclerosis is a disease of civilization, the data supports the applicability of the hygiene hypothesis to CNS autoimmune disease. This hypothesis proposes that the lack of serious childhood infections impairs development of an appropriately educated immune response. Imbalance of T-helper (Th1) and (Th2) responses and lack of regulatory T-cell populations are two of many proposed potential mechanisms for immune failures such as autoimmunity and allergy. It is also demonstrated that Mycobacterium bovis (BCG) infection, and lyophilized Mycobacterium tuberculosis all modify the course of clinical disease in mice induced for experimental autoimmune encephalomyelitis (a mouse model for human multiple sclerosis (MS)). All except the 18-kDa M. leprae antigen and the 19-kDa M. tuberculosis antigen are coded with very similar gene.
The nerve damage, a hallmark of leprosy previously thought to be due to the immune system's response to the leprosy bacteria, now seems to be a direct result of the leprosy bug attaching itself to specialized nerve cells called Schwann cells, the glial, or supporting, cells of the peripheral nervous system (PNS). Researchers also showed that M. leprae does not need to be alive to demyelinate nerve cells. Therefore, the knowledge gained by such M. leprae-induced myelin damage in the early infectious process provides valuable insights into the pathologic mechanisms of multiple sclerosis and other neurodegenerative diseases that destroy nerve cell insulation(3).

However, no research has hypothesized the possible involvement of mycobacterium leprae or its component in pathogenesis of MS. In this article, I will introduce the suggested pathway through which the mycobacterium leprae or its component enters CNS, then I will explain my hypothesis and I suggest how to evaluate it.

**The Role of vaccination and CNS disorders**

In light of a growing body of scientific information, vaccination exemption criteria ought to be expanded, especially in regard to infants, toddlers, and women of childbearing age. Despite using restrictive criteria, many studies have documented a relationship between vaccinations and adverse neurological sequelae (4-11).

Some of these studies focused upon febrile seizures during short time periods after various vaccinations. More recent studies have documented brain regions that are affected by febrile seizures (12-14). When a child is vaccinated; a complex process is initiated like a prolonged pulse of endogenously created interferon gamma (15). One of interferon gamma's most important effects is increasing permeability of tissues that normally have highly restricted permeability. Two such tissues are the intestinal tract and the blood-brain barrier. Interferon gamma is now realized to increase permeability in both of these tissues (16-19); and the increased permeability can have pathological significance. Intestinal permeability increased by interferon gamma can lead to increased translocation of pathogens (20); and increased permeability of the blood-brain barrier is associated with a variety of pathologic states, ranging from CNS-infiltration of peripheral pathogens, to CNS-entry of activated B-cells and T-cells of the human immune system (21-26).

It is suggested that mucosal administration of vaccines is an important approach for the induction of appropriate immune responses to microbial and other environmental antigens in systemic sites and peripheral blood. Mucosal immunity offers new strategies to induce protective immune responses against a variety of infectious agents. Such immunization may also provide new prophylactic or therapeutic avenues in the control of autoimmune diseases in humans (27, 28).

**Vaccinations and multiple sclerosis: The hygiene hypothesis**

The hygiene hypothesis is based on evidence that the imbalance of immunological response in childhood, specifically among the Th1 and Th2 lymphocyte subpopulations, is responsible for the development of some allergic and chronic diseases in the future. The deranging factor for the predisposition to future allergic response (Th2) is the obstruction of natural manifestations of infectious diseases (Th1 response) in young children. Evidence has emerged supporting the hypothesis that a reduction in antigenic stimulation brought about by widespread vaccination, improvements in standards of hygiene, and extensive use of antibiotics has contributed to the dysregulation of T-helper 2 cell (Th2) type responsiveness that typifies allergy. Regulation of the inherently Th2-biased mucosal immune response is crucial both to the maintenance of homeostasis at this strategic defensive barrier and to the prevention of allergic disease (1).

**The Hypothesis**

Multiple sclerosis has shown a dramatic and mostly genuine increase in incidence over the past 25 years in the industrialized countries. I suggest that MS is a syndrome of diseases, induced by intradermal BCG vaccine which may contain the antigen component resembling that of leprae that can either produce central demyelination by itself or by delayed hypersensitivity: The intradermal method bypasses the natural immunity barrier in epidermis and the mucosal aspect of the immune system; in addition to the immaturity of BBB barrier at time of vaccination allowing these particles to be sequestered in CNS. The elucidation of the mechanism responsible for the initiation of MS has obvious implications for the further development of specific therapies, or preventive measurement.

Such hypothesis will be discussed depending on the following data and illustrated in figure 1 and figure 2.

**M. leprae and M. tuberculosis**

The DNA sequences of secreted proteins of M. tuberculosis were compared with sequences of M. leprae. The genomic organization of genes for
secreted proteins is very similar in M. leprae and M. tuberculosis (2).

Most of the antigens of Mycobacterium leprae and M. tuberculosis that have been identified are members of stress protein families. Of the M. leprae and M. tuberculosis antigens identified by monoclonal antibodies, all except the 18-kDa M. leprae antigen and the 19-kDa M. tuberculosis antigen are strongly coded with very similar genes (2, 29).

**BCG and multiple sclerosis**

There is controversy as regard relationship between BCG and the course of MS; as mycobacterium tuberculosis (Mt), which is routinely used to promote the induction of autoimmune diseases, can also protect against their development (30). Data suggest that mycobacterial infection attenuates the severity of experimental autoimmune encephalomyelitis (EAE), at least in part, by promoting the apoptotic elimination of autoreactive CD4+ T cells (30). Also, a 12-kDa protein of mycobacterium tuberculosis protects mice against experimental autoimmune encephalomyelitis (31).

Shahram et al. (32) hypothesized that sympathetic nervous system (SNS) can be stimulated by pro-inflammatory cytokines such as TNF-α and IL1-β, production of which are induced by mycobacterial infection or mycobacterium components. Inhibitory effects of stimulated SNS on MS may occur via different ways such as inhibiting the production of pro-inflammatory cytokines and inducing the synthesis of anti-inflammatory cytokines, in other words, shifting the immune responses from type 1 toward type 2, as well as, induction of suppressor/regulator T lymphocytes, induction of heat shock proteins in brain and increasing the expression of Fas and Fas-ligand.

Ristori et al. (33) studied the effect of Bacille Calmette-Guérin (BCG) vaccine as an immunomodulator in MS. According to the guidelines for clinical trials in MS, a single crossover, MRI-monitored trial was performed in 14 patients with relapsing-remitting MS. After treatment, MRI activity was significantly reduced.

Nevertheless, risk of MS was inversely associated with a positive tuberculin skin test at age 7 years, i.e. with exposure to tuberculosis before the age of 7. This finding suggested a difference between MS patients and controls with respect to environment before school age, the former being less exposed to air-borne infections (34).

Additionally, other researchers reported that the clinical severity of EAE is enhanced by pre-treatment with BCG vaccine (35).

**Leprea bacteria and pathogenesis of demyelination**

In the May, 2002, scientists at Rockefeller University and New York University School of Medicine reported that the nerve damage that leads to a loss of sensation and disability of people with leprosy occurs in the early stages of infection (3).

The nerve damage, a hallmark of leprosy previously thought to be a by product of the immune system's response to the leprosy bacteria, now seems to be a direct result of the leprosy bug attaching itself to specialized nerve cells called Schwann cells, the glial, or supporting, cells of the peripheral nervous system (PNS).

The findings suggest that the body's immune response does not play a significant role in the early stage of neurological injury. The damage is characterized by the disruption of the myelin sheath, the insulation on nerve cell connections that helps transmit rapid signals between the brain and the peripheral organs, for example, skin and muscles. Damage to myelin causes loss of sensation, disability and paralysis.

The researchers found that, unexpectedly, M. leprae does not need to enter the cell to cause degeneration of the myelin sheath.

The researchers also showed that M. leprae does not need to be alive to demyelinate nerve cells. Similar results were obtained after cultured Schwann cells were exposed to bacteria that had been killed with radiation and to fractions of the bacterium's cell wall.

Previous research by Rambukkana, Salzer and their colleagues implicated a major component of the bacterium's cell wall called PGL-1 in its predilection for peripheral nerves, and they now propose that PGL-1 is a crucial cell wall molecule directly involved in nerve damage in leprosy (36).

**Evidence for CNS affection in leprosy**

There were researches reported CNS affection in leprosy. Detection of antibodies against phenolic glycolipid-1 (PGL-1), 35-kDa and 30-40-kDa components of mycobacterium leprae in the cerebrospinal fluid of leprosy patients were found; and some correlation was observed between the upper motor neuron signs and antibody positivity for 35-kDa and PGL-1 antigens in the CSF of these patients (37).

What is more, evaluation of the possible involvement of central optic pathways (COP) in leprosy patients with visual evoked potentials, in 37 patients with lepromatous leprosy and in 37 age-matched controls, revealed that the mean latency value of positive peak P100 in leprosy patients was significantly delayed compared to that of controls (38).
In addition, Jacob et al. (39), reported a case of 24-year-old man with Hansen's disease in Type 1 reaction, developed a demyelinating disorder affecting the central and peripheral nervous system. The neural damage could have been due to cross-reacting epitopes causing molecular mimicry and resultant demyelinating disorder. They hypothesized that post infectious encephalomyelitis results from a transient autoimmune response towards myelin or other self-antigens, possibly by molecular mimicry or by non-specific activation of non specific auto reactive T cell clones (40). T cells directed to microbial epitopes may recognize amino acid sequences shared with myelin antigens become activated and cross the endothelium of the BBB and attack the CNS myelin by molecular mimicry or along with antibodies (40, 41).

Clinical case evidence

Immune responses to heat shock or stress proteins are observed in several chronic autoimmune diseases. Such proteins are major antigens of many bacteria, especially mycobacteria. Birnbaum et al. (42) measured proliferative responses of lymphocytes from spinal fluids and bloods of patients with MS. Significantly increased spinal fluid lymphocyte responses to mycobacterial sonicate were present in 14 of 20 specimens from patients with MS (p < 0.025). Lymphocytes from 1 patient with MS responded only to M. leprae.

When patients with MS were classified according to duration of disease (< 2- or > 2-yr duration) 9 of 10 patients with recent onset had cerebrospinal fluid cells that responded to M. tuberculosis compared with 5 of 10 with longer duration symptoms (p < 0.012). Their data suggested a selective recruitment and/or expansion of mycobacterial reactive cells to the central nervous system of a subpopulation of patients with MS (42).

Evaluation of the hypothesis

My hypothesis could be assessed in vivo study, by exploring the presence of leprae particles in BCG vaccine, especially PGL-1 antigens. The methods which determine that there are homologous peptide sequences in leprae particles and myelin basic protein should be developed. Cultured oligodendroglia cells should be exposed to bacteria leprae and to fractions of the bacterium's cell wall for exploring the effect of this mycobacterium on such cells.

Then experimental studies on laboratory animals during their infancy period by examining the presence of leprae particles or components in CSF after subcutaneous BCG vaccination compared to CSF before vaccination.

An experimental study could be done on laboratory animals by injection of leprae antigens intrathecially and to assess if demyelination would occur in CNS and this to be compared to experimental autoimmune encephalomyelitis (a mouse model for human multiple sclerosis (MS)).

Human studies could be done by searching for leprae particles or PGL-1 antigens in CSF of patients with MS. A functional imaging depending on PGL-1 antigens could be invented for MS patients if clinically confirmed.

Conclusion

The aetiology of MS has been debated several times since the disease was first described. Epidemiological data suggest the notion that multiple sclerosis (MS) is an acquired autoimmune disease and the cause may be an environmental factor(s), probably infectious, in genetically susceptible individuals (43).

However, the major criticism of the autoimmune hypothesis is that autoantigen(s) specific to and causative for MS has never been identified. In addition, recent reports indicate that demyelination may precede inflammation (44, 45). Another intriguing idea regarding the aetiology of MS may be that the immune response in MS could result from a chronic infection rather than autoimmunity in the usual sense (46-47). So, this distinction between an autoimmune hypothesis and the microbial hypothesis may be more blurred than previously thought (48).

I suggest that MS is a syndrome of diseases, induced by intradermal BCG vaccine which may contain the antigen component resembling that of leprae that can either produce central demyelination by itself, as M. leprae does not need to be alive to demyelinate nerve cells, or by delayed hypersensitivity. If my hypothesis can be verified experimentally and clinically, then measurements to prevent MS disease could be accomplished.
Figure 1. The sequences of events leading to CNS affection due to childhood vaccination.
Of the M. leprae and M. tuberculosis antigens identified by monoclonal antibodies, all except the 18-kDa M. leprae antigen and the 19-kDa M. tuberculosis antigen are strongly coded with very similar genes. Intradermal BCG vaccine may contain the antigen component resembling that of leprae.

The intradermal method bypasses the natural immunity barrier in epidermis and the mucosal aspect of the immune system; in addition to the dysfunction of BBB barrier at time of vaccination allowing these particles to be sequestered in CNS.

M. leprae does not need to enter the cell to cause degeneration of the myelin sheath. M. leprae does not need to be alive to demyelinate nerve cells.

Antigen component resembling that of leprae can either produce central demyelination by itself or by delayed hypersensitivity.

Figure 2. The hypothesized pathway of how mycobacterium leprae or its components could be involved in the pathogenesis of CNS demyelination.
References