Infection as a cause of multiple sclerosis

Theories abound because no one knows the answers yet

It is difficult to think of an aetiological theory that has not been suggested to explain multiple sclerosis. Disconcertingly, however, many of the aetiological questions asked over 150 years ago are still unanswered.[1] Is the disease due to a vascular defect as initially suggested by Rindfleisch in 1863, who noted a blood vessel in the centre of each plaque, or is it a defect in the glial tissue as argued by Charcot in 1868 after he viewed and drew the glial and nerve changes under his microscope? Oppenheim was certain that multiple sclerosis was caused by environmental toxins. In the middle of the 20th century interest centred around the possibility that it was an immunological disease and, more recently, a genetic disease.

Perhaps the most enduring questions concern a potential infectious agent. In 1894 Pierre Marie, a former student of Charcot, argued strongly that infection was the cause of multiple sclerosis and that those who disagreed had not read his papers. He did not know the specific infective agent but was certain that a treatment would soon be available in the form of a "vaccine of Pasteur or lymph of Koch."[1] William Gowers and other writers believed that an infection could aggravate multiple sclerosis but was not the cause. There was a flurry of reports of virus and spirochete isolations and transmissions in the early decades of the 20th century, but none stood the tests of time and reproducibility. Absence of evidence is not evidence of absence, however, and the infection theory remained strong because it seemed to best fit the developing scenario. Every new antibiotic and antiviral agent is given a trial in multiple sclerosis. Viral infections have been suspected in clusters of cases, including the "epidemic"-like appearance and disappearance of a cluster of cases on the Faroe Islands.[2]

Intriguing epidemiological but weak virological and immunological evidence has resulted in a bewildering list of usual suspects including measles, rabies, scrapie-like agent, Carp agent, paramyxovirus, coronavirus, Epstein-Barr virus, herpes zoster, herpes simplex virus, human herpesvirus 6, rubella, mumps, canine distemper, Marek's Semliki forest virus, animal and human retroviruses, and human T cell lymphoma virus type I.[3] Although multiple sclerosis was on the top of the list of "most likely" when the concept of slow virus infection was being formulated in the 1960s, the transmission experiments were all negative. Interestingly, Stanley Pruziner, recent Nobel laureate for his work on prions, does not have multiple sclerosis on his personal list of possible prion diseases.[4]

Current scientific interest is focused on chlamydia pneumonia and the Epstein-Barr virus. Epstein-Barr virus has been under suspicion for over two decades, and recently it was noted that patients with multiple sclerosis had an increase in respiratory infections before the onset of multiple sclerosis and a fivefold increase over controls in infectious mononucleosis.[5] Is this an indication of a specific role for Epstein-Barr virus or just an indication of a non-specific response of the immune system in patients with multiple sclerosis?

A vascular theory for multiple sclerosis resurfaced with the development of anticoagulants, replaced in the 1960s by an interest in dietary therapies, which had a vascular defect as part of the rationale. Recent work is again focused on the vascular changes as a basis of the breakdown of the blood-brain barrier that precedes the inflammation and demyelination in a multiple sclerosis plaque. Proponents of the infection theory would add that an infection could be the initial event that precipitates this process.

Over the past century and a half, bolstered by a body of observations and anecdotes, proponents of aetiological theories have focused on environmental toxins, "neuropathic constitution," physical and emotional stresses, circulating myelinotoxins and lipolytic enzymes, dietary factors, and vascular thrombosis. Early writers all noted occasional cases in a family but dismissed these as coincidental. Recent research is convincing in showing the risk in siblings and fraternal twins to be about 2-5%, much higher than in the normal population, but about 30% in identical twins, a clear indication of a genetic factor.[6] But why don't the two thirds of genetically predisposed identical twins get the disease? The conclusion is that multiple sclerosis is a complex trait, determined by multiple genes and an environmental factor. Is the other factor an infection?

There has been a reluctance to dispense with any theory when the answer is still unknown. So a current popular overarching theory postulates a genetically predisposed individual who develops a viral infection that disrupts the vascular relations in the blood-brain barrier and initiates an immune reaction that continues as a waxing and waning destructive process that damages myelin, and perhaps more importantly in the long term, the axons. But just as a workable and testable theory has evolved, important work by an international group implies potentially four pathological patterns of multiple sclerosis.[7] So we must add to the quandary the possibility that we may be dealing with different disorders with different causes. No one ever said medicine was simple.

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