

## CLINICAL REVIEW

# Multiple Sclerosis: Epidemiological and Etiological Considerations

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### ABSTRACT

Multiple sclerosis (MS) is a disorder defined by damage to the myelin sheaths which surround axons and increase the speed of neuronal transmission within the brain and spinal cord. Slowing or dissipation of neuronal signals results in a broad range of impairments in motor and sensory functions, coordination of muscular activity, special senses and higher cortical functions. A key diagnostic feature of MS is that the deficits seen clinically are explained by a diffuse pathological process and not, for example, by a single lesion within the nervous system. The disorder affects about 50,000 Canadians and 350,000 people in the United States, mainly young adults between the ages of 15 and 45.<sup>1</sup> MS is a complex disorder resulting from the interaction of the host's immune system with an environmental factor (viral, bacterial or toxic); neither the genetic nor the environmental factors alone are sufficient to account for its incidence and course. Many advances in molecular biology and biochemistry have enhanced our current understanding of the mechanisms underlying the disruption of the myelin sheath. However, aspects such as the unique populations and geographical trends associated with MS have not been explained in the literature. This review explores the fascinating inter-relationships between geographic location, migration, genetics and environmental exposures in the development of MS.

### LATITUDE OF RESIDENCE AND THE DEVELOPMENT OF MS

In the early 1900s, a relationship between latitude of residence and the risk of contracting MS was identified.<sup>1</sup> In 1922, a second study conducted on soldiers in the United States found that MS was more common in men from the northern states, and in Europe, the chances of developing MS also increased with latitude.<sup>2</sup> In addition, a higher frequency of MS was found in countries with latitude greater than 40 degrees, both north and south of the Equator.<sup>2</sup> This latitude-dependent trend could be due to genetic susceptibility or an environmental factor.<sup>3</sup> However, the fact that most developing countries with less-developed healthcare systems are located in the tropical regions challenges the validity of this apparent trend, as the lower prevalence observed in these regions may be due to a dearth of diagnostic capabilities.

### EFFECTS OF MIGRATION ON THE DEVELOPMENT OF MS

Migrant studies suggest that a person's location of residence in childhood is of great importance in the development of MS, implicating an environmental factor. Adult

immigrants from northern Europe to South Africa have a higher risk of MS than Europeans who were born in South Africa or migrated there in early childhood.<sup>2</sup> The prevalence of MS in adult immigrants to South Africa was 62.2 cases per 100,000 people, compared to only 12.8 cases per 100,000 people in immigrants who migrated there between the ages of 1 to 14.<sup>5</sup> An Israeli study showed a similar result: the prevalence of MS was three times higher in Jewish immigrants from Europe or America than in those from Asia or Africa.<sup>3</sup> In another study, UK-born children with parents who are South Asian immigrants were found to have as high a risk as the white UK-born population. However, their parents retained the low risk from the country of origin, which also suggests that location of residence in childhood contributes more to the development of MS.<sup>7</sup>

A study tracking African and Asian immigrants to high-risk regions demonstrated similar findings: if an individual moves from a low- to a high-risk area in childhood, he or she acquires a higher risk of developing MS than a person who stays in the native country or who moves to a high-risk area as an adult.<sup>2</sup> Certain studies in Hawaii also found that the incidence of MS was higher in adult immigrants from areas of high risk than in childhood immigrants (one to 14 years

of age), suggesting that the environment encountered during an individual's childhood plays a vital role in the pathogenesis of MS.<sup>3</sup>

### **EFFECTS OF INFECTIOUS ORGANISMS ON THE DEVELOPMENT OF MS**

The risk of developing MS can change very quickly in a country, refuting the dominance of a genetically-based propensity in its pathogenesis. For example, clear records from many years prior to World War II demonstrated that there were no cases of MS in the Faroe Islands, Denmark, prior to the Second World War.<sup>6</sup> After the arrival of the British army, 24 cases were reported from 1943 to 1960.<sup>6</sup> The introduction of an infectious agent from the British Army is a plausible explanation.<sup>6</sup> Furthermore, contact with a small pet early in childhood has been associated with an increased risk of MS, again consistent with the idea that infectious agents may contribute in its development. However, further studies failed to support this notion.<sup>2</sup>

### **ENVIRONMENTAL EXPOSURES: VIRUSES AND BACTERIA**

In 1884, Pierre Marie proposed that an infectious agent was the cause of MS.<sup>13</sup> Since Marie's time, no studies have shown direct causality between an infectious agent and MS.<sup>13</sup> However, it is still possible that microorganisms play an indirect role, for example, by triggering immune-mediated attack on auto-antigens by activated T-cells, which can break down the blood-brain barrier.<sup>1</sup> Heat shock proteins, adhesion molecules and alpha-beta crystallin expression by oligodendrocytes and interferon (IFN) all play key roles in the development of MS plaques.<sup>1</sup> Many patients with MS have T-cells reactive to myelin binding protein (MBP), and the same T-cells are reactive to peptides on common viruses.<sup>14</sup> The 70-kDa heat shock protein of *Mycobacterium tuberculosis* and *Mycobacterium leprae* could act as an auto-antigen in MS, and mycobacterial 28-kDa surface protein can enter neuronal Schwann cells.<sup>14</sup> Indeed, the identity of the primary auto-antigen may vary between individuals.<sup>2</sup>

Precedents exist in other species for microbial organisms to directly cause demyelinating conditions, as shown by Visna virus in goats and sheep and Theiler's virus in mice.<sup>1</sup> As for humans, researchers have found herpes virus (HHV-6 and HHV-8 subtypes) in active MS plaques, and shown that oligodendrocytes preferentially express the HHV protein in MS plaques.<sup>1</sup> HHV is highly neurotrophic, and the same stressors associated with MS exacerbation, such as new illness, also cause HHV to reactivate.<sup>1</sup> Exposure to HHV in early childhood increases the chances of MS.<sup>1</sup> However, having an HHV infection in early childhood may be better than encountering it later in life, because, as in the case of Hepatitis B, later infections may be more likely to

lead to overt disease rather than a chronic asymptomatic carrier state.<sup>7</sup>

We might even say that early exposure is protective against developing the full disease later in life.<sup>15</sup> Other infectious agents show similar trends: inhabitants of developing countries, where EBV is encountered early in life, have low rates of MS compared to people in developed countries where EBV infection occurs later in life.<sup>7</sup> A Danish study showed that people with late EBV infection had almost three times higher risk of developing MS.<sup>16</sup> And, returning to the study of US Army recruits, young men from the low-prevalence southern states had much higher seropositivity to Epstein-Barr virus than those from the north, implying that a childhood encounter with the virus spared them from the full development of MS.<sup>17</sup>

### **THE "HYGIENE HYPOTHESIS"**

MS has been found to be more prevalent in countries with higher levels of sanitation, which led researchers to propose the "hygiene hypothesis" that excessive sanitation is a predisposing factor.<sup>9</sup> For example, even though inhabitants of northern latitudes have higher rates of multiple sclerosis, its incidence unexpectedly decreases in the arctic regions, which have low levels of sanitation.<sup>10</sup> Likewise, researchers believe that the lower prevalence seen in Japan may be due to the widespread use of "nightsoil" (manure) instead of inorganic fertilizers in farming.<sup>10</sup> Contamination of the food supply with this fertilizer may somehow deter MS from developing.

### **EFFECTS OF GENETICS IN THE DEVELOPMENT OF MS**

Apart from these multiple environmental factors, the epidemiology of MS is to some extent influenced by genetics. Studies show that individuals with Northern European heritage are more susceptible to the disease.<sup>1</sup> MS is more common in women than men, suggesting that the presence of two X chromosomes may somehow influence the risk of contracting MS.<sup>8</sup> Also, some ethnic groups have a much lower prevalence of MS than other ethnic groups living in similar environments. The Gypsies in Hungary, with ancestral roots in India, have a prevalence of 2 per 100,000 people, whereas the native European population has a rate of 37 cases per 100,000 people.<sup>2</sup>

Genetic studies in families with MS imply a heritable component to its pathogenesis: there is a higher risk between monozygotic twins than dizygotic twins, and siblings have a relative risk 20 to 40-fold higher than the general population.<sup>11</sup> Certain alleles of the HLA-Class II complex associate strongly with MS, in particular HLA-DR15w2 and DQw6, which are prevalent in northern Europeans.<sup>2</sup> Loci on the short arm of chromosome 6 (6p21) and chromosome 5 are also receiving increasing attention, and in some fami-

lies, incomplete penetrance of the genetic component is required to explain variations in incidence.<sup>2</sup> In summary, no single gene has been found to cause MS,<sup>11</sup> yet all these findings suggest that a hereditary predisposition towards MS is activated under certain environmental conditions and cannot be ignored.<sup>1,2</sup>

## CONCLUSION

MS is a complex disease with uncertain etiology. It may result from a genetic predisposition to certain defects in immune regulation, such as an intrinsic reaction to a self-antigen independent of any microbial factor. Yet MS is influenced by several environmental factors. A latitude-dependent trend is well-established, but we must consider other factors in explaining why incidence rates in some countries, like Japan, are such statistical outliers. Migrant studies have shown that country of origin may play a significant role, and certain infections in childhood may increase or decrease the risk. Currently, the search for the etiological source for MS continues. Recent advancements in genetics and molecular biology have elucidated pathological mechanisms amenable to modulation, allowing for the hope that this disease may be ameliorated or even cured. ✨

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