

## **MULTIPLE SCLEROSIS**

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Multiple sclerosis (MS) is the commonest cause of progressive neurological disability affecting young adults in our community. The disease usually commences as a discrete attack, known as a clinically isolated syndrome (CIS), which can affect any area of the central nervous system (CNS), that is the brain and spinal cord, but which most commonly attacks either the optic nerve, brain stem or spinal cord. These attacks usually develop over hours to days and are characterised by the influx of immune cells from the blood. These immune cells are generally thought to initiate damage within the CNS, consistent with the hypothesis that MS is an autoimmune disease in which the body's immune cells are inappropriately activated to attack target tissue, in this instance cells within the CNS.

Most clinically isolated attacks spontaneously remit over weeks to months but there is a significant risk of recurrence and with it, a formal diagnosis of MS, which is defined by the presence of two or more attacks that are disseminated both in space (affecting different parts of the CNS) and time (attacks that are separated by at least a month). There have been concerted attempts to understand the risk of developing subsequent attacks after CIS. This remains work in progress; the best we can do at present is to recognize that the risk of recurrence over the subsequent 10 years varies between 11-87%, depending upon the degree of abnormality detected on magnetic resonance imaging (MRI) scans of the brain.

There are three major subtypes of clinical MS that are recognized. The majority of people are formally diagnosed as having MS at the time of the second attack when they are specified as having relapsing-remitting MS. Between 50-75% of patients with relapsing-remitting disease will eventually enter another sub-type of the disease known as secondary progressive MS, which is characterized by inexorable progression of neurological disability; transformation from relapsing-remitting to secondary progressive disease occurs, on average, between 10 to 15 years after disease onset. The third sub-type of disease is known as primary progressive disease, which is characterized by inexorable progression of the disease from its onset. The average rate of progression of primary and secondary progressive disease is the same, suggesting common drivers of neurodegeneration in these instances.

Despite intensive study, the cause of MS remains unknown. What is clear is that MS is a complex condition in which genetic, environmental and stochastic factors all play a part.

In recent years approximately 54 regions of our DNA have been shown to harbour genes that influence the susceptibility to MS. There has been considerable confusion in both the scientific literature and lay press concerning what these discoveries have told us about MS and how they will assist in patient management. Firstly, it is clear that some of the identified regions overlap with regions already known to predispose to other autoimmune diseases such as diabetes, rheumatoid arthritis and thyroid disease. This discovery both supports the autoimmune hypothesis of MS and also provides an opportunity to understand what is common between the various autoimmune diseases and what drives individual susceptibilities to one disease as opposed to another. Secondly, it has been widely assumed that the genetic studies have identified individual genes within the susceptibility regions that actually drive disease. In general, this is not the case, as the relevant regions often harbour multiple genes, many of which could rationally influence disease susceptibility; much of our

work over the next few years will need to be directed to understanding which of the various candidate genes is actually the responsible agent. Thirdly, whilst these discoveries have provided insight into population-based susceptibilities, they do not provide us with useful information to accurately define the risk of MS for any given individual. Nevertheless, the genetic data are likely to provide us with important new leads concerning the drivers of MS and hence new treatment opportunities. Another important challenge is to work out how the various susceptibility genes interact, which will provide new insights into how the disease is initiated and whether this differs for different subpopulations of people at risk for developing the disease.

We now also have an emerging understanding of the environmental factors that contribute both to the susceptibility to the disease and to its subsequent activity. Of particular importance has been the identification of contributors to the increased incidence and prevalence of the disease amongst those residing in high latitude regions. These contributors include relative Vitamin D deficiency and reduced exposure to ambient ultraviolet light, the latter being the principal determinant of the former but also probably providing additional, independent influence that is mediated by mechanisms other than through Vitamin D metabolism. Another contributing environmental influence is the Epstein Barr virus (EBV), although it is important to recognize that most of the normal population is exposed to this virus; this has led to the assumption that it is the timing of the exposure and the nature of the immune response to the EBV that dictate the susceptibility to MS, with those developing frank infectious mononucleosis being most susceptible. On balance, it would seem that exposure to the EBV might be necessary but that this, by itself, is insufficient to drive susceptibility to the disease. Another important susceptibility factor is smoking, which also appears to contribute to disease activity once it is initiated, important information for people with MS when considering life-style choices that might impact upon their disease.

Additional factors known to contribute to the risk of relapses in the short-term include systemic infection and pregnancy, with the risk being reduced in the third trimester but equivalently increased for the first three post-partum months. Despite much debate, there remains no compelling evidence that either trauma or immunizations contribute to disease activity, at least at the population level.

Current available immunomodulatory treatments successfully target the relapsing remitting phase of the disease to reduce both the risk and severity of relapses. It remains unknown as to how much these agents, when delivered during relapsing remitting MS, influence either the subsequent risk of developing secondary progressive MS or, alternatively, its tempo. On the other hand, none of the currently marketed therapies commenced during progressive MS has been convincingly shown to alter its course, suggesting that the therapies inadequately target the important pathogenic factors that are operative during this phase of the disease.

There is general consensus that the spectrum of available therapies needs to expand to agents that will provide either neuroprotection or regenerative capacity. Here the challenge is to not only to develop relevant therapeutic agents that can adequately access the CNS but also to provide robust mechanisms by which to test their efficacy in proof of concept studies. Other extant needs include the development of robust biomarkers that will enable accurate prediction of the likely disease course and which

can be used to reliably track both the extent of damage and the ongoing level of disease activity. Such innovations will be vital if we are appropriately target more potent but potentially more risky therapies to those at greatest risk of disease progression.

In summary, whilst MS remains an enigmatic disease, it is clear that very significant therapeutic benefits have been delivered to people with MS over the last 20 years. An emerging deeper understanding of the aetiology and pathogenesis of MS should provide opportunities for further significant therapeutic advances over the next decade.