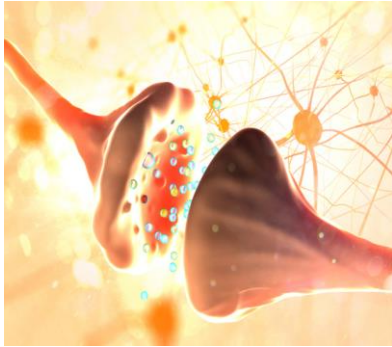


UNRAVELLING THE CAUSES OF MS



20 June, 2017

In MS, the brain and spinal cord are mistakenly attacked by our own immune system. This involves autoimmune processes that specifically damage the myelin which forms an insulating layer around nerve fibres. Myelin allows the electrical signals to travel rapidly along the nerves, damage to this myelin leads to a delay or block in the flow of electrical signals. This leads to the symptoms of MS that can include numbness, weakness, visual loss and mobility problems.

Exactly what triggers this autoimmune process in each individual is unclear. However, we do have very good evidence on some of the factors that can contribute to the development of MS across the population as a whole.

These are a combination of genetic and environmental risk factors. Risk factors are features about a person's biology and life that can contribute to the chances of developing a disease. Each of these factors alone does not mean a person will definitely get MS, but collectively they can increase the likelihood that someone will get MS – and the exact combination of risk factors is likely to be different in each individual.

Understanding the risk factors for MS also helps us to understand the biology of the disease and how we might better treat it, as well as prevent it.

WHAT IS A RISK FACTOR?

Risk factors are anything or any exposure that increases the likelihood of developing MS, but they are not the direct or only cause of MS.



Genetics and ethnicity

MS is not considered a classical genetic disease in that there is not one single gene that causes MS. Rather, there are over 110 different known genetic factors which contribute to MS. It has been estimated that genetics may account for around half of the risk of MS, and those with a family history of MS are at greater risk than the general population. Even so, the majority of people with a family member with MS will not develop the disease – so genes on their own are not enough.

Most of these 110+ genetic factors, each only contribute a very small part of the risk of MS, although one immune system gene, known as HLA-DRB15*01 is known to contribute a much larger part of the genetic risk. This gene is also more commonly found in people of northern European ancestry, which also partially explains why these populations are more likely to develop MS than people with other ethnic backgrounds. Many of the other more minor risk genes may also play a role in regulating the immune system, but more research is needed to fully understand their role. These genes may also influence the way we respond to the other environmental, or lifestyle, risk factors.



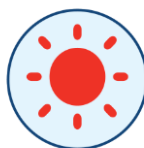
Gender

There are clear gender differences when it comes to immune disorders. Estimates suggest about 8% of the population are affected by autoimmune diseases and of those approximately 78% are female. In Australia, three times more women than men develop MS. Scientists have shown that this gender difference is not apparent in cases of MS that occur before puberty and after menopause, showing that it is likely to be the sex hormones that influence the immune system in a way that contributes to the development of MS – research is underway to understand this more fully.



Viral infections

One virus shown to have the strongest connection to MS is the Epstein Barr virus (EBV). This virus is commonly associated with glandular fever, however the majority of the population are infected with EBV in childhood with only mild, non-specific viral symptoms. While approximately 90% of the general population has been infected with EBV, it is believed that almost 100% of people with MS have been infected (often unawares). Although nearly everyone will be infected with EBV in their life, not everyone will develop MS – again showing that EBV is not sufficient in itself to trigger MS.



Climate and sun exposure

Where you live can also influence your risk of developing MS. The further you live away from the Equator, the greater your risk of developing MS – this is called the 'latitude effect'.

In Australia, those living in northern Queensland are 7 times less likely to develop MS than those in Tasmania. One explanation of this is that sunlight, or more specifically exposure to ultraviolet (UV) radiation, decreases with increasing distance from the Equator. Ultraviolet light is known to have a myriad of effects on the human body, including direct effects on the immune system and also playing a key role in the synthesis of vitamin D.



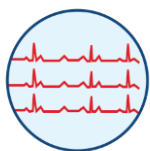
Vitamin D

Most of the vitamin D we need is made in our body in response to sunlight. Lack of sunlight, or low UV exposure, leads to vitamin D deficiency, and many studies around the world have strongly linked low vitamin D levels in the blood with the development of MS. As a result, MS Research Australia is carrying out a large clinical trial testing whether vitamin D supplements could prevent MS in people at high risk, and if so, what dose is best. Results from this trial, expected in 2019, should give us key insights into the role of vitamin D in the development of MS.



Smoking

Numerous studies have shown that smoking significantly increases your chances of developing MS. Smokers, and people exposed to second hand smoke, are almost two times more likely to develop MS and more likely to develop progressive forms of MS. For people who already have MS, there is good evidence that stopping smoking reduces the risk of disability progression. Smoking is known to cause an increase in inflammation and chemicals in smoke can also directly alter the function of some immune cells, potentially contributing to the development of MS.



Stress

Some studies have linked stress with the risk of developing MS, however, people's different coping mechanisms and response to stressful events make this connection difficult to confirm. Studies that have looked at the loss of a child or other major life events which are universally stressful for everyone, have found a only a weak connection to the development of MS. Australian researchers have also shown that serious illness or personal

injury either to yourself or a close family member can lead to an increased risk of developing MS. Other studies have linked the severe stress associated with war for example, with an increase in MS relapses.



Diet and physical activity

There is a great deal of interest in the role that nutrition and diet may play in the development and also the management of MS. Dietary studies are complex due to the many potential nutritional components found in our diets. This makes it difficult to isolate the influence of a particular diet or any single dietary factor. There is evidence that keeping cholesterol and fats in the blood within a healthy range may lead to better disability outcomes for those with MS, however this is an area of research which is ongoing.

There is stronger evidence when it comes to body weight and obesity and the risk of MS. Numerous studies have shown that being overweight/obese, particularly during adolescence, is associated with a 2-3 fold increase in the risk of developing MS. It is also associated with worse outcomes in people who have MS.

Lack of physical activity may also be a risk factor in developing MS but the results are very varied, possibly due to the difficulties in accurately getting people to recall their physical activity across earlier years. But we do know exercise can have a positive effect on body weight, overall health and well-being, as well as having direct benefits for brain health.

Summing it all up

So, in conclusion, how does MS develop? Well it is a complex interaction between genetics and the environment. Of course, how you respond to your environment depends on your genetics. Your genetics determine how your immune system responds to an EBV infection, how you process vitamin D and which sex hormones you have also influence your immune system. Your sun exposure determines how much vitamin D your body makes and smoking adds additional inflammation into an already volatile mix. Diet, physical activity and stress may also contribute to this mix. Potentially, there are other, as yet unknown, factors which may also lead to an increase in inflammation or be able to mimic or add to the role of some of the factors listed here.

Only a few of these factors may come together in some individuals to trigger MS. In others it may be an accumulation of many of these risk factors together – the combination will be different in different people. There is no doubt that MS is a complex and varied disease. Through research we have come a long way to understanding these complexities. In 2016, there was an international workshop assessing and summarising the extensive knowledge

of the factors that contribute to MS and their report was published in the *Multiple Sclerosis Journal*. This consensus will now help us to start acting with further targeted research and, importantly, advice and guidance to the community on how we can go about reducing the risk of developing MS.

Risk Factors can have different effects on MS, they can enhance the risk of developing MS and/or increases the risk of disease progression once MS has developed. The evidence supports the risk of developing MS, but research is ongoing in both areas. The table below is adapted from work by Professor Robyn Lucas of the Australian National University, an expert in epidemiology and public health.

	Risk of MS	Risk of disease progression
Genetics	***	•
Gender	***	*
EBV infection	***	X
Low sun Exposure	***	•
Low vitamin D levels	***	**
Smoking	***	***
High animal fat Diet/ low Exercise	•	•
High Body Mass Index	**	•
Stressful events	•	•
*** Strong Evidence ** Medium Evidence • Low Evidence X No link found * Males are more likely to be diagnosed with progressive MS.		