

A New Disease Model for MS

Ashton Embry

A disease model is a hypothesis for what causes a disease and how it progresses. A model is developed using all the available empirical data which have accumulated for the disease and combining that with theoretical knowledge gained from studying many diseases. The key aspects of a viable model are that it explains all important observations, is theoretically reasonable and is as simple as possible.

One of the major contributions of a good model is that it allows new understanding of the disease process and points the way to potentially effective treatments. Given a model's influence on the research effort and proposed/employed treatments for a given disease, it is important to reappraise the model as new data become available. Such reappraisal can take the form of either a minor modification of the model or possibly a complete overhaul, depending on how well or badly the new data fit with the existing model.

Over the last 160 years, many disease models have been proposed for MS but none have led to development of an effective treatment. This suggests we are still awaiting the development of a reasonably realistic model which incorporates the key factors that are causing and driving MS.

Over the past 50 years, two models have received the lion's share of attention and research funding - the infection model and the autoimmune model. The infection model proposes that MS is caused by either a bacterial or viral infection in the central nervous system. However, the continued failure to identify a causative infectious agent, despite many detailed studies, has downgraded this model such that it now receives little support.

Currently, the preferred disease model for MS is that it is a cell-mediated, autoimmune disease. This model has the immune system becoming sensitized to parts of myelin due to both genetic susceptibility and a viral infection such as Epstein-Barr (EBV). It is also proposed that a defect in immune regulation is needed to promote the

initiation and continuation of autoimmunity and vitamin D deficiency is one of the favoured causes of such decreased immune regulation. Over time, repeated autoimmune attacks on myelin eventually cause clinical symptoms and MS is diagnosed, usually in early adulthood.

This model has been preferred because over the years it has done the best job of explaining the available data for MS, including many diverse, epidemiological, genetic and immunological studies. Also, an experimental animal model, called experimental autoimmune encephalitis (EAE), reproduces many features of MS and thus adds further support to the autoimmune disease model. Using the autoimmune model as a foundation, developed therapies have focused on suppressing or modulating various parts of the immune system.

Over the past 20 years, dissatisfaction with the autoimmune model has grown as new observations, which cannot be easily explained by the model, have accumulated. Some of the important data which have raised doubts about the autoimmune model include:

- 1) Current immune-based therapies have little, if any, effect on disease progression.
- 2) Neurodegeneration appears to be an important part of MS throughout disease development, becoming dominant in the latter stages.
- 3) Detailed pathological studies of newly developed lesions have demonstrated that myelin disintegration precedes the invasion of the immune system indicating immune action is secondary.
- 4) MS lesions are venocentric and often are associated with iron deposits
- 5) Immune activity sometimes occurs associated with the optic nerve where no myelin is present.
- 6) No autoimmune activity occurs in the peripheral nervous system where myelin is also present.

These observations have not led to any serious reappraisal of the autoimmune model mainly because no one has been able to provide a better model which would explain these data as well as all the other data which seem to support the autoimmune model.

Little over a year ago, the important observation that most people with MS have impaired venous drainage from the brain (CCSVI) became

widely known. Notably, this finding was not compatible with the autoimmune model, especially given the finding that the venous malformations responsible for CCSVI preceded the MS disease process. These new data, which have now been solidly confirmed by venography on thousands of MS patients, have led to the development of an entirely new model for MS.

In this CCSVI model, extra-cranial, venous blockages cause altered blood flow in the brain which in turn results in myelin breakdown in various ways including oxygen deprivation (hypoperfusion). It is also hypothesized that the altered flow leads to iron deposition in the walls of veins, consequent breakdown of the blood-brain barrier, the introduction of noxious elements into the CNS, and consequent neurodegeneration. Immune involvement is seen as part of the clean up process by a normal immune system.

Presently, a war of words is going on between the supporters of the conventional, autoimmune model and those that favour the upstart CCSVI model. Notably both sides use observations which are not compatible with their opponents' model to argue against it. For example, the autoimmune model supporters use the common presence of a specific immune gene, immune dysregularities, and the requirement of an EBV infection, to discredit the CCSVI model. They also make the valid argument that some cases of CCSVI do not result in MS. The CCSVI model supporters use the established presence of venous blockages and altered blood flow, as well as the six points which had previously raised doubts about the autoimmune model, to disparage it.

Given a valid model has to incorporate all the important data, both the autoimmune and CCSVI models are not valid because they both fail to include critical data. Clearly, a new disease model for MS is required. It must honour the data which had formed the basis of the autoimmune model but must also include the key observations related to CCSVI. The key aspect of this model is that two independent conditions - CCSVI and immune dysregulation - must occur for MS to develop. Notably both of these pathologies depend on both genetic and environmental factors for their manifestation.

In this “two to tango” model, CCSVI gradually erodes the integrity of the blood-brain barrier which contributes to neurodegeneration and also allows the dysregulated immune system access to the CNS. This results in an abnormal immune reaction to disintegrating myelin and eventual permanent damage to the nerve axons themselves. The strength of both CCSVI and the immune dysregulation will vary greatly between individuals and hence very different presentations of MS would be expected. For example, those with lesser immune dysregulation may not experience an immune-related, relapsing and remitting phase and may be diagnosed with a progressive course driven mainly by CCSVI-related neurodegeneration.

Given this new, improved model, the best way to treat MS is to:

- 1) Upon diagnosis, be tested and treated for CCSVI
- 2) Use nutritional strategies to counter any immune dysregularity and to promote vascular health
- 3) Consider using an MS drug to help counter immune activity only if the actions of points one and two fail to halt disease progression.

We have to hope the scientists and clinicians who deal with MS will put aside their prejudices and allegiances to the drug companies and acknowledge the autoimmune model is no longer valid. Only then will they realize that their current research and treatment strategies for MS need to be completely rethought and changed.