Genetic Epidemiology and Causal Factors of MS

By Ashton Embry

I have always been somewhat surprised at the low level of interest by the MS research community in identifying the causal factors of MS. It seems to me that the best path to finding effective treatments for MS lies in finding out what causes it in the first place. There certainly were no effective treatments for infectious diseases until science discovered that micro-organisms such as bacteria and viruses were the causal factors of such diseases. Sadly, I suspect one of the reasons why little effort is being made in this field is the widely accepted dictum of the pharmaceutical industry "There is no money in a cure!"

Another likely reason why causal factors are not hotly pursued is that the only experiment that could identify a causal factor beyond any doubt would be to expose a group of people to suspected causal factors and see if they get MS. For obvious reasons this is never going to happen. So, to get at causal factors, historical scientific methods have to be employed and these usually entail epidemiological work which most MS researchers have no interest in. Epidemiology entails finding out everything you can about people who already have MS. Things like where they live, where they were born, what they eat, what infections have they had, what % of a given population has MS, all can help ferret out causal factors.

The good news is that a few researchers are trying to get at the causal factors of MS and one of the leaders in this field is Dr George Ebers, the chair of the neurology department at Oxford. He came to Oxford after a distinguished career in Canada where he did, and continues to do, a lot of genetic epidemiology. Genetic epidemiology looks at the rates of MS in persons who are genetically related to persons with MS or who have had long, close contact with persons with MS when they were growing up. Such information can tell us a lot about the nature of the causal factors of MS.

The classic genetic epidemiology work has been to study MS in twins, both identical and fraternal. Twins of course share many environmental factors during childhood and adolescence and identical twins have the same genetic makeup whereas fraternal twins only share 50% of their genes. They found that, for identical twin pairs with at least one having MS, both twins have MS in about 30% of the sets. For fraternal twin sets, both have MS in only 4% of the sets. This finding leaves no doubt that genes play a major role in MS and that only genetically susceptible persons get MS. On the other hand these results also tell us that one or more environmental factors are involved because for most sets of identical twins in which one has MS, the other one doesn't. If MS was purely genetic, when one identical twin had MS, the other would too.

Dr Ebers and his colleagues then asked the question whether or not environmental factors specific to a family were involved in MS. They answered this one by studying the rate of MS in adopted siblings of persons with MS. Such individuals would share the same family environmental influences but none of their genes. They found that adopted siblings had the same rate of MS as the general population in Canada and this strongly suggested that specific family environmental factors were not involved. The researchers also studied half siblings of persons with MS and this population included those who shared the same home with the person with MS when they were growing up and those who did not. It was found that both groups had the same rate of MS which was about half of that of full siblings. This confirmed the lack of specific family related environmental factors and

supported the conclusion that environmental factors which affect the population at large are driving MS.

Such a robust conclusion is very helpful because there just are not that many factors which affect the population at large, result in a very similar rate of MS along a given latitude and can contribute to the initiation and progression of an autoimmune disease like MS. The obvious ones are common infectious agents which can activate autoimmune immune cells, common foods which can activate or suppress immune cell activity, sanitation which determines the overall exposure of the population to infectious agents and the consequent "education" of the immune system, and vitamin D supply from sunshine and/or fish which determines a person's ability to adequately regulate an autoimmune response. Notably these are exactly the same factors which I identified though a deductive exercise using the principles of evolutionary biology in concert with the known disease mechanisms (i.e. activation and failed suppression of autoaggressive immune cells).

One recent genetic epidemiological study involved looking at identical twins at different latitudes and seeing if latitude influenced whether both or only one twin got MS. It was clear that sets of twins with both having MS were much more common in higher latitudes than in lower ones. This added more support to the concept that vitamin D supply is a major causal factor in MS.

The genetic epidemiological results from the identical twins also tell us that in Canada only about half of the people who are genetically susceptible to MS actually contract the disease. This comes from the result that 30% of identical twins both have MS. Thus, out of a group of 10 identical twin sets with at least one with MS (i.e. 20 genetically susceptible individuals), only 13 will have MS and 7 won't. Of course there must be some identical twin sets that are susceptible to MS and neither have MS. This would bring the overall rate of MS in susceptible individuals down to about 50%.

This begs the question of, if the environmental factors are affecting the population as a whole, why don't all susceptible people in that population get MS. The answer to this question lies in the timing of exposure to the causal factors. The best explanation of why at least half the susceptible individuals do not get MS is that at least one of the factors must vary greatly in time and likely interact with another factor which only acts over a short time interval. Thus it would take a coincidence of timing of the two factors to cause MS and it appears such coincidence happens about half the time in Canada. Of the above factors, the obvious ones that fulfill these requirements are vitamin D supply which is high in summer and low in winter in Canada (and Britain) and an initial infection with a cross reactive agent which occurs over a short interval of time.

Putting everything together it is hard to escape the interpretation that MS is caused by an infection with a cross reactive virus or bacterium in a child or adolescent with a low vitamin D level (most likely from October to May in Canada). The need for a coincidence of the two factors nicely explains the 50% rate for genetically susceptible persons getting MS in a high latitude country like Canada where vitamin D supply is low to negligible for at least 8 months. Of course the MS contraction rate will decrease with decreasing latitude and consequent higher vitamin D supply over more of the year. The longer most people are protected against MS by adequate vitamin D over a year, the lower the MS rate. Thus in low latitude areas (e.g. northern Australia) few genetically susceptible persons get MS.

Is such a causal scenario without doubt? No it is not, but it is solidly supported and makes complete sense of all the known data. It is by far the best explanation of the cause of MS. However I estimate it will be at least 10 to 20 years before most MS researchers and clinicians accept that MS is

fundamentally a long latency, vitamin D deficiency disease. A few classic examples of the long time it takes conventional medicine to accept an obvious causal factor of a disease include lack of sun exposure causing rickets (100 years), gluten consumption causing celiac disease (40 years) and a bacterium causing ulcers (12 years).

It is not hard to understand such resistance. When the causal factors of a disease are correctly identified, current approaches to research and treatment must be radically altered. Most people, especially researchers and clinicians, will fight long and hard against anything that would precipitate that much stressful change in their careers. Such is the genetic nature of human beings.