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Review

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Factors predisposing to the development of multiple sclerosis

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Summary

Multiple sclerosis (MS) is a chronic neurological disease, which is known to be more common in UK than many countries. While there are multiple genetic factors affecting risk of developing MS and disease severity within the condition, evidence on the rising worldwide prevalence and the increasing female to male preponderance has focused interest on environmental factors influencing MS risk. Data on several of these factors are reviewed, with particular focus on those such as vitamin intake, smoking and obesity, which may be influenced at a personal and population level by medical advice.

When patients ask what has caused their illness, they are usually referring to the aetiology rather than the pathological basis. For example, people with multiple sclerosis (MS) asking about the cause of their condition are not interested so much in T-cell abnormalities and other immune dysfunction as knowing some of the factors that may have predisposed them to develop this autoimmune condition. The aim of this article is to review the data on MS risk factors, with particular emphasis on those which may be modifiable through medical advice at a personal and population level.

Epidemiology

The worldwide incidence of MS is rising, and is currently estimated to be about 3.6/100 000 person-years in women and 2.0/100 000 person-years in men.[1] The female preponderance, common to many autoimmune diseases, is increasing, from an estimated 1.4 in 1955 to 2.3 in 2000.[1] MS is particularly common in UK, with an incidence of 7.2/100 000 in women and 3.1/100 000 in men.[2]

Genetics and migration data

Much MS risk is known to be genetic, with particular HLA patterns, such as DRB1*1501 (HLA DR15), conferring higher risk. Many genes have been identified for predisposition to the disease or severity level within diagnosed populations.[3] This genetic element accounts for the higher disease risk in first-degree relatives of people with MS. For example, the Danish series found an excess lifetime risk of 2.5% for first-degree relatives, to be added to the general population sporadic risk (0.5% in females, 0.3% in men).[4] However, much risk must be environmental, as shown by the lack of complete concordance for MS between identical twins.[5]

The epidemiological data discussed above shows that MS risk varies between countries, with some such as the UK clearly being a relatively high risk area. This variation is not due solely to the differences in gene pools and ethnic mix between countries. The clue that the geographical differences in MS reflect environmental as well as genetic factors comes from migration data. Migrants going from low- to high-risk areas (such as UK) maintain their

lower risk status but this protection does not extend to their UK-born children. Those going from high- to low-risk areas experience decline in risk closer to that prevalent in their final residence, and the decrease appears greater for those migrating in early childhood. It could be argued that migrants differ in health, socio-economic status and access to health care from native populations, but this cannot explain all the findings, such as variation in MS risk among migrants in USA.[6] There must be environmental factors, probably most potent during childhood, which interact with genetic predisposition to influence MS risk.

Environmental risk factors

The migration data and geographical differences in MS risk have interplayed with various theories about infectious exposure altering MS susceptibility. Many different agents have been proposed, too numerous to discuss.[7] One theoretical model could be termed the hygiene hypothesis; that MS is triggered in susceptible individuals who experience infection with common pathogens not in infancy, but later in life at a different stage of development of their immune systems. Exposure to common pathogens in early childhood is normal and confers no higher risk of later autoimmune disease. Some data exist suggesting that late infection with Epstein–Barr virus (EBv) is a particularly relevant agent i.e. having a history of later mononucleosis confers higher risk than asymptomatic EBv in early childhood, or indeed being part of that small proportion of the adult population who are EBv negative. Combining the data on HLA status and EBv infection would lead one to predict that MS risk would be greater in subjects who had a genetic risk, e.g. HLA DR15, and evidence of EBv exposure. A case–control study of 148 women with MS and 296 age-matched healthy controls showed that being HLA DR15+ and having a elevated (>1:320) anti-EBNA-1 titre increased relative risk of MS to 9.[8]

Examination of high- and low-risk areas shows a pattern related to latitude. Why should there exist geographical differences in MS such that residents of higher latitudes have increased risk, even among people of comparable genetic background?

There are many factors associated with latitude but one attracting increasing research interest is sunlight exposure. Studies indicate that residence in a high sunlight area or outdoor work reduce MS mortality, that MS prevalence is inversely correlated with altitude (which relates to sunlight intensity) and that people with MS have lower than expected skin cancer mortality rates (see figure 1).[9] However,

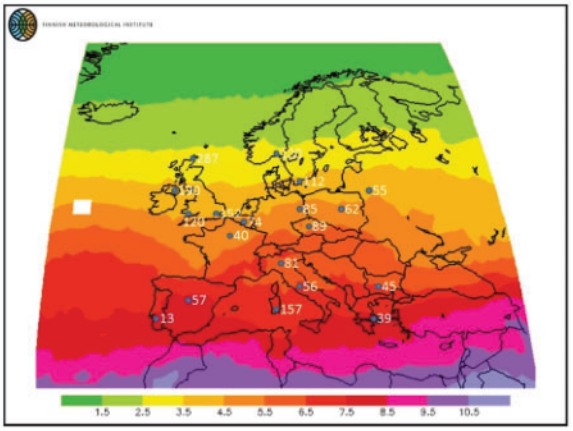

Figure 1. End-of-summer noon UV index and MS prevalence. UV index is from 15th September 1985 with superimposed prevalence data for MS across Europe. Dean G, Yeo TW, Goris A, Taylor CJ, Goodman RS, Elian M, *et al.* HLA-DRB1 and multiple sclerosis in Malta. *Neurology* 2008; **70**:101–5. PROMOTE: Long-Term Multi-Sensoral UV Record. [http://promote.fmi.fi/] Accessed 16 August 2009. Figure cited from Handel AE, Handunnetthi L, Giovannoni G, Ebers GC, Ramagopalan SV. Genetic and environmental factors and the distribution of multiple sclerosis in Europe. *Eur J Neurol* 2010; **17**:1210–4.

there are many alternative explanations for these findings. If a mechanism could be established by which sunlight exposure could directly influence MS risk, this would strengthen the argument for causation rather than association. One such mechanism concerns vitamin D. Sunlight exposure is important for the cutaneous synthesis of vitamin D3, which is subsequently hydroxylated in liver and kidney to the active hormone $1,25(OH)_2$ vitD. At high latitudes, levels of the active hormone decline during winter. 25(OH)D is the readily measurable precursor form of the vitamin, levels of which are known to vary with season and diet. This variability in serum levels over time means a large longitudinal study with repeated sample collection is required to examine whether serum 25(OH)D predicts MS risk. Intelligent use of samples taken for other reasons provides invaluable data.

Two hundered fifty seven military personnel with confirmed MS, having at least two serum samples taken before onset of symptoms and stored in a military serum repository, were identified. Each case was matched (age, sex, race) with two random non-MS controls. Sample sizes were adequate for white participants and for these, there was a 41% decrease in MS risk for every 50 nmol/l increase in 25(OH)D [Relative risk (RR) 0.59, 95% Confidence intervals (CI) 0.36–0.97, $P=0.04$].[10] These data, while supportive of a protective effect of vitamin D on MS risk, could be explained by association [i.e. a

common factor reduces MS risk and increases 25(OH)D] rather than causation (i.e. low vitamin D increases MS risk). Support for the latter hypothesis comes from the Nurses' Health Study, which pooled data from about 190 000 women followed for 10–20 years and examined diet, including vitamin intake, and MS risk. Analysis showed that those with the highest quintile of vitamin D intake had 0.67 risk compared with the lowest quintile. Those with intake of vitamin D of at least 400 IU/day had 0.59 risk compared with those with no supplemental vitamin D.[11]

These data, combined with other studies on vitamin D, animal models of MS and immune studies in humans, suggest that vitamin D may well play a role in MS susceptibility. However, there must be other causal factors interacting because low 25(OH)D levels are common in the population, yet MS remains a relatively rare condition, with a lifetime risk from birth of receiving an MS diagnosis estimated at about 5/1000 in women and less than half of that in men for the UK population.[2] The role of vitamin D supplementation in decreasing MS risk (including for offspring of people with MS, through supplementation during pregnancy), and in reducing rate of progression in confirmed MS, as well as the key questions of the required dose and potential toxicity, are topics of considerable interest. A phase I/II, randomized, controlled trial of high-dose vitamin D with calcium supplementation, administered for 1 year in people with MS, has been recently reported. The primary endpoint was serum calcium levels, which remained normal in both treatment and control groups, but the secondary endpoints of relapses and T-cell proliferation showed benefits in favour of vitamin D supplementation.[12]

Other individual risk factors

The question of causation of MS would not be comprehensively reviewed without discussion of lifestyle choices which affect MS risk. One such is cigarette smoking. This is a risk factor with strong evidence of causality where doctors can confidently advise patients to modify behaviours without concern of adverse effects e.g. vitamin D toxicity or impracticality e.g. moving latitude. There are four prospective studies of MS risk and smoking. The largest of these was the Nurses' Health Study of over 200 000 American women, which showed that smoking is associated with an increased risk of MS. For example, relative incidence rate for women with 25 or more pack years compared with never smokers was 1.7 (95% CI 1.2–2.4. $P < 0.01$). The data showed an increasing MS rate with increasing pack years and held after adjustment for age, latitude and ancestry.[13] The other three smaller studies showed convergent[14–16] results but with 95% confidence intervals not excluded chance. Furthermore, these results are in keeping with several retrospective studies and with the adverse effects of smoking on risk of other autoimmune diseases like lupus. When advising people already diagnosed with MS who currently smoke, there is emerging work reporting that smoking affects the risk of conversion from relapsing remitting to secondary progressive MS, and that the clinical course of MS is worse in smokers.[17]

The second individual factor implicated in MS risk is obesity. Again this finding comes from analysis of the prospective Nurses' Health Study, to examine the relationship between body mass index (BMI) at age 18 with risk of subsequent diagnosis with MS. Obesity at the age of 18 years (BMI > 30 kg/m^2) more than doubles the risk of MS [multivariate relative risk (pooled) = 2.25, 95% CI 1.50–3.37, P for trend <0.001].[18]

Conclusions

In summary, MS results from an interplay of environmental causal factors acting in conjunction with genetic susceptibility. Exciting new research suggests that some of these environmental risk factors may be amenable to modification by medical advice. Further work is needed to strengthen our understanding of these risk factors and how to best advise our patients with MS and the wider population.

Key points

- Risk of MS is influenced by genetic factors, only some of which have been identified.
- Risk of developing MS varies between countries and migration data suggests that only some of the inter-country variation can be explained by genetic factors.
- In UK, the incidence of MS is high compared with world figures. Nevertheless, the overall lifetime risk of being diagnosed with MS is low at about 5/1000 in women and less than half of that in men.
- Large-scale epidemiological analyses suggest that vitamin D supplementation, smoking and obesity may influence MS risk, but the underlying mechanisms require further research.

Conflict of interest: None declared.

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