Russell W Brain and the aetiology of multiple sclerosis- a historical perspective

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Acronyms:

MS: Multiple sclerosis
CNS: Central nervous system
EBV: Epstein-Barr virus
UVB: Ultraviolet B
Introduction

The legacy of British neurologist Russell Walter Brain (1895-1966) to the field of neurology is difficult to overestimate. His seminal work as the principal author of Brain's Diseases of the Nervous System (1933), as the editor of the medical journal Brain (1954-66) and as President of the Royal College of Physicians (1950) continues to influence modern neurological education and practice. In a landmark review published in the Quarterly Review of Medicine in 1930, he gives a critically important account summarising ideas of the time thought to underlie the then called “disseminated sclerosis”, a disease he notes to be, “after syphilis, the most frequent disease of the nervous system” in the UK\(^1\). Across a century and a half, vast progress has been made in attempting to elucidate the as yet unknown cause of MS, which is unravelling to be multifactorial, highly complex and likely dependent on both genetic and environmental risk factors\(^2\). In this report we aim to evaluate the relevance today of what we believe to have been an important perspective on MS, with a focus on Brain's ideas on the aetiology of the disease; many of which have stood the test of time.

Geographical distribution of MS

Brain discusses the varying geographical prevalence of MS and observes the disease to be common in North America (where it is thought to be greater in north-eastern states near the Great Lakes) and Europe (noting a particularly high prevalence of MS in England, Norway and Switzerland and a relatively low prevalence in Romania and Italy). This is in line with the well characterised latitudinal gradient of MS whereby MS prevalence increases with increasing distance from the equator\(^3\). This has been demonstrated across northern Europe as well as in individual countries including the UK, Scotland, the United States and Australia, where multiple sclerosis is almost seven times more prevalent in Hobart, Tasmania (40\(^\circ\) south) compared to Queensland, Northern Australia (10\(^\circ\) south)\(^4,5\). This distribution of MS has implicated vitamin D deficiency in its aetiology
as sunlight intensity and duration, and subsequent serum vitamin D levels, are negatively correlated with latitude.

Of intrigue, it has recently been suggested that the latitudinal gradient of MS is decreasing\textsuperscript{6,7}. A meta-analysis found that whereas a latitudinal gradient of MS prevalence in Europe and North America has remained over time, this is not the case for a latitudinal gradient of incidence\textsuperscript{6}. It is possible that previous work demonstrating a latitudinal gradient has been confounded by diagnostic resources, or alternatively that a disappearing latitudinal gradient of MS incidence is a reflection of a change in environmental risk factors such as greater migration between countries or vitamin D levels (reduced through increased sun avoidance and rising body mass indices in the developed world). However, in light of the fact that a latitudinal gradient of MS incidence has nonetheless persisted in New Zealand and Australia, comparing environmental factors in these southern continent countries with countries in Europe and North America may help further understanding of what underlie the latitudinal gradient\textsuperscript{6}.

In considering the ethnic distribution of MS, Brain notes a higher American incidence of MS among foreign-born individuals compared to native US individuals. He refers to an analysis of 70 foreign-born patients in New York in which it was found that the occurrence of MS is low in Russians and Italians whereas, in contrast, English and Germans had twice the expected number of cases, Swedes 2.5 times the expected number of cases and Norwegians 3.6 times the expected number of cases. Migrant population studies have provided great insight into the influence of migration on disease risk and have demonstrated a changing incidence of MS in migrant groups which occurs over one or two generations. This period of time is too short to explain the changing MS risk through genetic susceptibility. It is generally thought that individuals who migrate from a low risk to a high risk MS region during early adolescence (approximately prior to age 15 years) will adopt the susceptibility of the local environment, in contrast to those who migrate in adulthood who tend to maintain the risk associated with their country of origin\textsuperscript{8}. It may be speculated that the individuals studied by Brain were post-adolescent and would have maintained the risk profile of their original country.
This phenomenon enables identification of environmental factors which may influence MS risk pre-adolescence and which vary as individuals migrate. Indeed, given the high latitude and consequent widespread vitamin D deficiency in Northern Europe, particularly Scandinavia, this region poses a high MS risk, arguably greater than that which would be expected elsewhere including in North America. Alternatively, these observations may be explained by a viral infection which has varying spread in different countries. One postulated infectious agent is Epstein-Barr virus infection which is thought to contribute to increased MS risk, particularly at an adolescent age of infection\textsuperscript{9}.

**Demographic distribution of MS**

Brain states that MS is seemingly less prevalent in black compared to white individuals which has, until recently, been a long-standing perception. A study of the large US military veteran population of the Gulf War era between 1990 to 2007 reported a steady increase in MS risk in black individuals, and a subsequent black to white relative MS risk ratio of 1.27\textsuperscript{10}. This is supported by further study of a US military cohort between 2002-2009 which found a 1.5 times greater incidence rate of MS in black compared to white individuals\textsuperscript{11}. These American findings are not only in contrast to Brain's observation but also to the post-world war II era where among world war II and Korean conflict veterans, white men were found to have almost double the MS risk compared to black men\textsuperscript{12}. These recent findings highlight a changing racial demographic profile of MS. It is currently thought that the racial distribution of MS in countries of high latitude has changed and that black individuals may have a greater risk of MS compared to white individuals. An important consideration is that dark-skinned individuals living in countries at high latitude are exposed to environmental conditions in stark contrast to those to which their ancestors adapted. Dark skin is more abundant with melanin, a pigment which determines human skin color and absorbs Ultraviolet B (UVB) radiation. Melanin effectively competes for UVB radiation which is required for vitamin D synthesis in the skin, leading to less efficient vitamin D synthesis in dark-skinned individuals\textsuperscript{13}. 
At high latitudes where UVB radiation and vitamin D levels are particularly limited, and likely compounded by lifestyle changes over time such as increased time spent indoors, this may contribute to an increased MS risk in dark-skinned races.

Moreover, Brain interestingly reports a male to female sex ratio of MS at the time of three to two. A finding in North Switzerland of an almost reversed sex ratio leads Brain to speculate that local environmental conditions may influence the sex ratio and that “investigation of which might provide a clue to the aetiology of the disease”. Whereas MS was considered to be a predominantly male disease in the early 20th century, perhaps the most marked change in the epidemiology of MS in the last century is a change from a predominantly male disease to a predominantly female disease. The current sex ratio of MS has clearly illustrated a rising female preponderance of the disease with some reports of sex ratios of more than 3 females per male14. Improved access to healthcare and diagnosis in women may in part explain a changing sex ratio, but are unlikely to account for its entirety in light of the substantial time spans so far investigated. As illustrated by a recent meta-analysis of studies to date, a rising female preponderance of MS is a largely global phenomenon confirmed in cohorts from for example the Netherlands, Canada, Crete, Iran, the UK and Japan14-20. It is however not a universal finding as a rising female preponderance has not been shown in Sweden, generally considered a region of high MS risk, where the Swedish MS register has shown a consistent sex ratio of about 2.6 females to 1 male with no evidence of a gradual change21. Elucidating how the altered lifestyle of women over a number of decades interacts with identified risk factors of MS is likely to be a useful avenue in exploring the underlying mechanism of both the sex ratio and cause of MS.

**An infectious aetiology of MS**

An infectious aetiology of MS has been long proposed and is widely considered in Brain's review. He rejects claims by researchers who believe that they have transmitted MS as a neurotropic infection to animals. He believes instead that the limitations of these studies were substantial
(particularly inadequate controls) and that the findings were unsupported by histological examinations. He notes that the responsible “pathogenic agent must be such as to produce circumscribed lesions, mainly if not exclusively perivascular in distribution, and attended by perivascular infiltration with plasma cells and lymphocytes”. He considers the possibilities that the infective agent may be present in the central nervous system (CNS) or that the MS lesions may be a consequence of toxin exposure, either endogenous or exogenous in nature. He finds it difficult to reason the characteristic features of the effects of a toxin to the pathological changes observed in MS and doesn't find this plausible, but instead takes the view that MS is the consequence of a neurotropic infection. He is largely sceptical of proposed agents but instead considers a judgement to be premature with regard to both the identity and route of dissemination of the pathogen. Numerous subsequent studies investigating possible infectious agents have resulted in infection by the human-γ herpes virus EBV garnering substantial support for a proposed involvement in MS aetiology. EBV is a ubiquitous virus and 90–95% of adults worldwide are infected, but it usually remains asymptomatic in a latent state with intermittent reactivation and lytic replication. Conclusively determining if the currently strong association between EBV and MS truly represents a relationship of association or causation, and by what method and where EBV would influence MS pathophysiology, remains largely debated today. This discussion is limited by inconsistent findings and varying and imperfect methodological techniques.

Genetics of MS

Brain addresses the observed clustering of MS within some families, although rightfully regards this to be an extremely rare finding relative to sporadic MS. He finds that the occurrence of two affected siblings is the most common within MS clusters and that MS within two successive generations is more infrequent. He recognises the possibility of misdiagnosis in some of these cases and indeed highlights instances of this. He explains that these observations and the lack of cases across successive generations may suggest that this most likely reflects shared environmental
exposure, with virtually no role for inherited predisposition. Of note, he would go on to change his view and acknowledge a potential influence of genetic factors further on in his career.

Shared environmental exposures within families are likely to in part contribute to an increased MS risk among relatives. However, the identification of 110 disease susceptibility loci to date which each exert a small increase in disease risk indicates a role for genetic susceptibility to MS\(^{23}\). An increased MS risk in closer biological relatives of MS (but not in adopted first degree relatives, half-siblings or spouses) demonstrates that an increased MS risk in families can not be explained solely by shared familial environment, but suggests a significant genetic contribution\(^{24}\).

**Conclusion**

At a time of a far advanced understanding of the clinical features and risk factors of MS, and rife causation theories, Brain's review demonstrates the importance of thoughtful evaluation of current ideas in generating a comprehensive evaluation of a field at a current point in time. Brain's observations highlight the changing epidemiology of MS over the last century which are likely to provide the platform in striving towards elucidating MS causation, notably a suggested reduced latitudinal gradient of MS incidence, an increasing female-to-male sex ratio and an increasing disease rate in dark-skinned compared to light-skinned individuals. Unconvinced by theories of causative roles by factors such as cold, heat, trauma and metallic poisoning, Brain seemingly aligned with the view that an infectious aetiology of MS is likely, yet his observations were also to foresee the proposed roles for vitamin D deficiency and genetic predisposition in MS risk. He ends his review by saying that the relapsing-remitting nature of MS “may, when its cause is fully understood...lead to the cure of the disease”. In addressing how any proposed hypothesis for the pathophysiology of MS may underlie the disease course, it is critical to determine if identified risk factors can account for the clinical features of MS, for example through the recurrent reactivation of a latent virus. Therefore, it seems, his conclusion was as apt in 1930 as it is today.
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References:


