Ethnicity and multiple sclerosis – moving beyond preconceptions

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Abstract
Historically, Multiple Sclerosis (MS) was thought to be substantially more common in individuals from European ancestral backgrounds. Recent studies have challenged this preconception, with a concerning increase in incidence among Black British and African American individuals. In this review we provide a brief overview of the evidence for ethnic variation in MS risk, summarise potential explanations for this variation, and illustrate how these observations could be used to provide potential insights into disease biology.

Multiple Sclerosis (MS) is a complex autoimmune disease of the Central Nervous System (CNS) that affects ~0.1% of the population and is a leading cause of disability in young people. The pathogenesis of MS is thought to involve an interplay between genetic factors – of which the MHC type II allele HLA DRB1*15:01 is the most potent – and environmental risk factors such as smoking, early life obesity, Infectious Mononucleosis (IM), and low serum vitamin D [1]. Historically, MS was thought to be substantially more common among individuals of European ancestry than in individuals from other ethnic groups and ancestral backgrounds. This view is being challenged by more recent studies demonstrating a concerning increase in the incidence of MS among Black British and African American individuals. Here we provide a brief overview of the evidence for ethnic variation in MS risk, summarise potential explanations for this variation, and illustrate how these observations could be used to provide potential insights into disease biology. It is worth emphasising upfront that there is an important distinction between 'ethnicity' – a subjective label which incorporates an individual's national, cultural, religious, and physical identity – and 'ancestry', a more objective term which describes the origins of the genetic variants inherited by an individual. Both ancestry and ethnicity are correlated to an extent with genetic risk factors and the environmental milieu to which an individual is exposed. As all individuals carry genetic material derived from different ancestral populations, attempting to characterise an individual's ethnic background is intrinsically an oversimplification. This oversimplification is worth bearing in mind when considering large-scale epidemiological studies in MS, which typically focus on reported ethnicity rather than genetically-determined ancestry.

Prevalence of MS in minority ethnic populations

Several cross-sectional observational studies have reported a higher prevalence of MS in individuals of Northern European ancestry. This observation appears robust both when comparing prevalence between countries, and when comparing ethnic groups within the same country [2,3]. The Global Burden Of Disease study reported the highest age-standardised prevalence of MS in Northern America (164.6/100,000) and Western Europe (127.0/100,000), with the lowest rates seen in Sub-saharan Africa and Oceania (<5/100,000) [4]. A large cross-sectional study of individuals of White, Black, and South Asian ethnicity in the UK found adjusted prevalence rates of 180/100,000, 74/100,000, and 29/100,000, respectively.[2]

Prevalence estimates reflect both the rate at which new diagnoses are made (incidence) and the mortality rate. Differences in disease prevalence between groups could therefore be due to differences in incidence or in mortality – either directly related to the disease process, or at a wider population level. Additionally, relatively small changes in disease incidence take time to impact on prevalence, and remain influenced by population mortality. The lower reported prevalence of MS in people from minority ethnic backgrounds could be explained by either lower incidence or higher mortality in this population subgroup, or may result from a combination of the two. Bias in diagnosis leading to later diagnosis and/or falsely lowered incidence may also impact on population prevalence. There is evidence that mortality is higher in individuals with MS from Black British/African American ethnic backgrounds under the age of 55 [5], and cognitive biases have the potential to impact both the time to diagnosis and the absolute number of diagnoses in minority ethnic populations. Prevalence and incidence estimates for MS are also confounded by both access to diagnostic facilities (e.g. MRI scanners) and data quality, and these factors make it difficult to draw strong conclusions for some parts of the world, including Sub-saharan Africa, Latin America, and much of Asia [4].

Incidence of MS in minority ethnic populations

Recent incidence data have challenged the historic view that MS is predominantly a disease affecting White individuals. Data from the cohort of US military veterans serving in the Gulf war period (1990-2010s) reported that MS incidence in this cohort was higher among individuals of African

American ethnicity (12.1/100,000 person-years) compared to White individuals (9.3/100,000 person-years) [6]. Various potential explanations for this observation have been postulated: military personnel are predominantly male, are exposed to a peculiar mix of environmental exposures which may increase the risk of MS non-uniformly across ethnic groups (e.g. close contact with others which may facilitate transmission of EBV, irregular shiftwork, noxious chemicals, intense physical labour etc), may be subject to increased medical attention, better health insurance plans, and may be more likely to seek medical help with subtle weakness/incoordination due to high physical conditioning, all of which may introduce a diagnostic bias. Furthermore, this is a young cohort, and it is possible that individuals from different ethnic groups are more likely to manifest with, or be diagnosed with MS at different ages. Recent data from our group in East London demonstrate that the odds of MS are greater among Black British individuals than White British individuals below the age of 30 [7]. The observation of higher MS incidence in minority ethnic individuals has also been made in the Kaiser Permanente Cohort from the USA, which reported incidence rates of 10.2/100,000, 6.9/100,000, 2.9/100,000, and 1.4/100,000 for Black, White, Hispanic, and Asian individuals respectively [8]. Generally, these data suggest that the incidence of MS among people of African ancestry living in the USA and UK may be equal to, if not higher than, individuals of European ancestry.

Mechanisms of ethnic variation in MS risk

'Ethnicity', as recorded and measured in observational studies, is variously presented as a composite measure of self-identified social grouping along lines of national, ancestral, or cultural tradition. It is an intrinsically vague concept, especially when based on self-report, which serves as a noisy proxy measure that an individual may share certain genetic and environmental risk factors with a certain group. The advent of biobank-scale datasets which collect genotyping/sequencing data and detailed phenotypic data, such as the UK Biobank, permits a genetically-based definition of ancestry, often defined by genetic principal components, to complement data on self-reported ethnicity.

Explanations for ethnic variation in MS risk can be broadly divided into hypotheses about why there might be real variation in genetic and environmental risk factors between ethnic groups, and hypotheses about why this observation may be an artefact. Clearly, disparities between ethnic groups in terms of healthcare access and language proficiency, and unconscious (or conscious) diagnostic biases on the part of treating clinicians may bias towards lower MS incidence in minority ethnic populations. This is a particularly pertinent consideration in countries such as the US where access to healthcare is highly correlated with ethnicity, and minority ethnic groups are less likely to have health insurance coverage [9].

Various biological reasons may explain ethnic disparities in MS incidence. Ethnic variation may be a proxy for geographical variation. There is a well-established latitudinal gradient in MS incidence and prevalence, with MS incidence increasing as latitude increases. This gradient can be observed both between and within countries, and so could feasibly either explain or be explained by ethnic differences in MS incidence as people from different ethnic groups are non-randomly spread across a country. Latitude may itself may be a proxy for either environmental variables (e.g. vitamin D, sun exposure, UV light, pollution, affluence, EBV infection), or genetic factors (i.e. MS susceptibility alleles which vary in frequency between populations).

Geographical location cannot entirely account for the association between ethnicity and MS. Migration studies have highlighted that geographical location prior to adolescence is the key determinant of MS risk, with first generation migrants assuming the MS risk of their new homes if they migrated before adolescence, but retaining the MS risk of their countries of origin if they migrated in adulthood [10]. It appears that second generation immigrants to "high risk" countries such as Denmark have an MS risk that is significantly higher than their parents, and potentially even higher than that of the country to which they have migrated [10]. Second, even in fully 'admixed' populations, in which people from different ethnicities live in roughly the same areas for roughly the same period of time, MS incidence rates still appear to differ, suggesting that geography alone cannot explain the variation [2,3].

It is feasible that certain behaviours or environmental risk factors associated with MS risk, such as smoking, may be more or less common in certain groups. Additionally, it may not be possible to overcome residual confounding by factors which may influence MS risk such as household crowding and socio-economic status which may explain subtle differences between individuals living in geographically similar areas. In fact, some environmental factors may interact with ethnicity, in that their effect on MS risk may either be potentiated or blunted in certain ethnic groups, as we have recently suggested for Infectious Mononucleosis and smoking based on data from an East London GP cohort [7]. Third, it has been suggested that higher MS incidence among Black individuals in some studies may be explained by lower vitamin D levels, however this has not been borne out by the empirical data [11,12].

Despite mounting epidemiological evidence that MS incidence in individuals of Black ethnicity may be as high, if not higher, compared to White individuals, genetic studies of MS have focused on individuals of European ancestry [13-15]. The few studies which have examined genetic determinants of MS susceptibility in individuals of non-European ancestry have recapitulated the strongest association signal in Europeans at the Major Histocompatibility Complex (MHC) locus. These studies have not yet discovered novel loci but have broadly supported the view that the direction and magnitude of genetic effects does not differ substantially between populations for many established MS risk variants, with a couple of intriguing exceptions [16-18]. Understanding the genetic architecture of MS susceptibility in non-European groups – particularly individuals of African ancestry – will improve our understanding of the causes of MS in all individuals, may lead to identification of new drug targets, and may help pave the way for personalised diagnosis, prognosis, and treatment of MS.

Concluding remarks

Contemporary epidemiological data have overturned the historical notion that MS is predominantly a disease of White individuals. Clinicians should be aware of the increase in MS incidence among individuals of non-European ancestry, specifically among people with African ancestry and ensure they do not fall prey to the misconception that a diagnosis of MS is less likely if an individual is not in a "traditionally" high-risk group. Studying MS in ancestrally diverse populations can help to expand our understanding of disease biology, particularly with respect to the role of, and interactions between, genetic and environmental risk factors. Importantly, including individuals of all ancestries in MS research ensures that advances in diagnosis and management of MS are equitably shared by all persons with MS regardless of ethnic background.

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