The major cause of multiple sclerosis is environmental: genetics has a minor role - No

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Rebuttal

Ethical and practical considerations mean that virtually all studies considering the aetiology of multiple sclerosis are observational (epidemiological) rather than interventional; in this context, association does not necessarily imply causation, and it is hard to sustain belief in any statement that suggests that ‘the major cause’ for multiple sclerosis has been established. In his classic essay on the relationship between epidemiological association and causation Bradford Hill noted that when the strength of an association (the odds ratio attributable to an exposure) was substantial, causation was highly likely. However, he also pointed out that a substantial effect was not essential, and that even when the strength of an association was slight the implicated exposure might still be genuinely causal.1

In the epidemiology of multiple sclerosis there are no known exposures (environmental or genetic) where the observed odds ratios are substantial; certainly nothing anywhere near the level suggested by Hill as providing compelling evidence for causation. Because environmental exposures are generally quantitative and the strength of such effects are often described in terms of a comparison between the most discordant individuals, there is an inevitable tendency for the odds ratio reported in connection with environmental effects to be inflated in comparison to equivalent genetic exposures, where effects are usually reported on a per-allele basis. The resulting impression that the odds ratios attributable to environmental factors are more substantial than those attributable to genetic variation pervades the epidemiology of multiple sclerosis. However inspection of the observed odds ratios, even without allowing for the disparate ways in which these are measured, shows that in reality there is little difference between them; and, in fact, taken in aggregate, currently known genetic factors account for far more variance in disease risk than is attributable to suggested environmental effects.2, 3

Furthermore when comparing these exposures it is appropriate to bear in mind the attendant difference in the reliability of the claims for associations.4 Unlike genetic factors, environmental exposures tend to vary in intensity over time and are often difficult to measure with accuracy, as a result association analysis can be readily confounded by selection bias and reverse causality can easily generate false positives.

Because the power of an association analysis is critically dependent upon the frequency of the tested exposure as well as its strength, the apparent importance of one factor compared with another is likely to be critically dependent upon the population studied. For example, consider the inborn error of metabolism phenylketonuria (PKU) in which the ingestion of phenylalanine leads to developmental brain damage in individuals who are homozygous for genetic mutations that inactivate phenylalanine hydroxylase. In a population where the mutant allele is uncommon and everyone eats phenylalanine epidemiological analysis will suggest that the disease is entirely genetic. On the other hand, in a hypothetical population where everyone is homozygous for the mutant allele but only some people eat phenylalanine the same condition would appear to be entirely environmentally driven. In this particular condition, both factors are necessary but neither is sufficient and the apparent importance of one rather than the other is entirely determined by their relative frequencies. This hand wavy example serves to illustrate the fact that association studies provide only a subjective guide as to the relative importance of aetiological factors. These power issues mean that epidemiological association may be impossible to identify for necessary causal factors that are excessively common or sufficient factors that are extremely rare.

In keeping with Mackie’s notion that most effects have a ‘plurality of causation’ and in the absence of any reliable evidence for necessary or sufficient causes for multiple sclerosis it is logical to conclude that the ‘causal’ exposures identified by epidemiological analysis to date are in fact what Mackie described as INUS condition: Insufficient to cause the effect on their own but a Non-redundant
(i.e. essential) component of a set of factors which resulted in the effect; this set of factors being an Unnecessary (in the sense that many other sets of factors can also result in the effect) but Sufficient cause. By way of illustration consider the situation in which Mr Smith fails to put out his cigarette before leaving the house, following which the cigarette sets light to the furniture and the house burns down. In this case we can correctly conclude that ‘the forgotten cigarette caused the house to burn down’. However other factors also contributed (e.g. the flammable furniture), many house fires occur in the absence of cigarettes and most of the time forgotten cigarettes do not cause house fires. In the case of house fires a forgotten cigarette is neither necessary nor sufficient, but may be contributory.

The facts of the matter are that relatively few environmental factors have been implicated to date, the odds ratios attributable to these are little different from those claimed for individual risk alleles and the evidence supporting their association is decidedly less robust. In making the comparison between environmental and genetic influences it is also important to acknowledge that the aetiological insights provided by genetic associations are significantly obscured by our currently limited understanding of their functional consequences. In the absence of this information genetic associations seem remote, intangible and therefore more difficult to appreciate than more easily understandable environmental factors.

There can be no doubt that by identifying exposures which are associated with the development of a disease epidemiology can provide invaluable insights into aetiology. In which context, even if the motion were true, and genetics only made a tiny contribution to aetiology, or only accounted for a fraction of a percent of familial clustering, the tacit implication that the aetiological clues provided by the robust associations established through careful and systematic genetic analysis should be ignored, seems illogical. The aetiology of multiple sclerosis is certainly not solved but the good news is that genetic and environmental studies seem to be converging and are providing real clues; the future looks extremely promising.

References