MS and heat

The smoke and the fire

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We are all creatures of the sun. Increasingly, studies emphasize the complex interplay between our environment and our neuroimmunologic systems. Both brain and immune system start out largely nonspecific and receive much of their exquisite complexity through a nature–nurture dynamic. Both learn as they go and remember what they have seen. Multiple sclerosis (MS) is a complex disease at the interface of this dynamic; prevalence and progression vary greatly; its etiology remains elusive. Disease progression is commonly reflected as recurring bouts of inflammatory disease activity leading to axonal demyelination and loss, gliosis, and secondary (Wallerian) degeneration. The cumulative burden of this activity, some of it clinically silent, eventually surfaces in chronic disability.

With etiology still incompletely elucidated, MS is the result of a complex and dynamic interplay among genetic, immunologic, and largely unknown environmental factors. Those genes with a link to MS susceptibility all encode immune function. While we all carry the T cells that perpetuate MS, only 1 in 1,000 appears to have the particular, at least partly acquired, signature of immune reactivity that leads to MS. It is well-established that MS prevalence is characterized by a geographic latitude gradient, often attributed to sun exposure and vitamin D, but itself manifest in genetically susceptible populations.[1] The latitude gradient is waning,[2] a change more readily attributable to the environment than genetic factors or sampling bias. This is largely driven by higher incidence rates at lower latitudes, possibly fueled by increased industrialization, less sun exposure, and lower childhood infection rates due to increased hygiene. While latitude, vitamin D, viral exposure, and temperature all associate with the sun, it is important to distinguish environmental factors affecting MS susceptibility from those that affect MS severity and patient function. High ambient (and body core) temperatures contribute to pseudorelapses, a worsening of symptoms in the absence of active disease. Causes of worsening can be difficult to distinguish, and are a common source of confusion among both patients and physicians, making studies on environmental modulation of performance particularly valuable.

In this issue of *Neurology*®, Leavitt et al.[3] present both cross-sectional and longitudinal data, showing associations of cognitive performance to temperature in MS. Cognitive performance was worse in warmer temperatures in patients with MS, but not healthy controls; and a decline in cognitive performance over 6 months was associated with a temperature increase, i.e., performance was worse if the temperature rose. This study on a New Jersey cohort is based on cognitive tests of processing speed and memory. Their findings are consistent with previously established seasonal links to disease activity on MRI.[4]

Reports of seasonal dependence of MS are not new. Seasonal effects have been reported for immunologic markers,[5] relapses,[6] and MRI activity.[4] The effects are modulated by geographic locale, but vitamin D and sun exposure, seasonal viral prevalence, and seasonal immune reactivity keep emerging as possible explanations. The study by Leavitt et al.[3] differs in 3 important respects: 1) it provides, albeit limited, longitudinal follow-up; 2) it uses cognitive assessment as a marker, more sensitive than the commonly used MS disability scores; and 3) it studied a patient cohort outside the relapse pattern, during periods of putative disease quiescence.

The study findings are mixed tidings for clinical trials: while the use of cognitive dysfunction as a sensitive surrogate for MS disease activity is welcome, the list of potential confounders of MS activity markers keeps getting longer. These confounding factors complicate trial design, especially as trials are becoming smaller and shorter through increased reliance on surrogate endpoints. Now, cognitive performance joins the ranks of markers subject to annual fluctuations that potentially bias clinical trials, as do relapse rates and MS lesions. How can we reliably and affordably capture highly dynamic subclinical disease activity that is detectable with sufficiently frequent

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MRI,[4,7] but still evades routine clinical screening? We know about the serious limitations of the standard Expanded Disability Status Scale (EDSS) score as marker for progression.[8] The authors suggest that cognitive performance may be a superior surrogate measure, with greater sensitivity to otherwise subclinical disease, because focal lesions are more likely to affect complex distributed neural networks than motor or sensory function. Indeed, cognitive impairment tends to be more highly correlated with MRI findings than is EDSS.[9] However, in designing clinical trials it is important to consider additional factors besides temperature that can influence cognitive functioning, including affective state.[10]

Finally, correlation is not causation. Studying modulators of complex dynamic processes is hard, comparison difficult, bias from undercorrected or overcorrected confounding factors likely, particularly in a cross-sectional approach, making longitudinal data especially valuable. Where temperature stands in the causal chain of MS etiology and symptomatology remains unanswered, at least for the moment. Is the observed cognitive decline a consequence of new disease activity or merely an expression of heat sensitivity from existing disease burden? Heat-triggered conduction delay is an established characteristic of demyelinated axons and the basis of cooling therapy in MS.[11]

The testing of cognitive function, rather than more common motor function based clinical assessment, is a valuable addition to the tools used to unravel the complex modulations that influence the seasonality of MS. More comprehensive testing for subtle cognitive impairment can also complement the persistent sensorimotor emphasis in clinical assessment. Such emphasis is historically understandable, as any disease is first characterized by its symptoms, and their treatment and assessment will likely continue to influence our choice of surrogate markers. But this and other emerging evidence reminds us that the smoke is not fire, although both relate to heat.

DISCLOSURE

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