It is all but 50 years since Sir Donald Acheson proposed a relationship between solar radiation and multiple sclerosis (Acheson et al., 1960). The subsequent discovery of the link between sunlight and vitamin D raised the potential for dietary supplementation to prevent or ameliorate the most common chronic neurologic disease of young adults.

Research in the field has proceeded down two distinct lines: epidemiological studies aimed at confirming and refining the association; and studies directed towards providing biological plausibility that may advance association to causation or at least justify large-scale clinical trials with an inexpensive agent. If definitive evidence is represented by a completed jigsaw puzzle, many pieces have been added to this story but others are missing and the picture is still indistinct.

It is clear that multiple sclerosis results from the interaction of genetic susceptibility with environmental factors. The strongest clue to an environmental candidate is the correlation with latitude—prevalence increasing with distance from the equator—for which the clearest data come from Australia where the disease is seven times more prevalent in Tasmania compared with tropical Queensland in populations of similar genetic background (McLeod et al., 1994). Ultraviolet sunlight-dependent metabolism provides the major source of vitamin D3 (D3) in humans and at high latitudes solar radiation in winter is too low to produce it in adequate amounts. Replicated evidence now exists for a correlation between the risk of multiple sclerosis and reduced sunlight exposure (Freedman et al., 2000; van der Mei et al., 2003; Islam et al., 2007; Ebers, 2008) although interpretation is influenced by uncertain knowledge of the critical period(s) of environmental effects in the pathogenesis of the disease: in utero, in childhood or throughout life. The evidence is significant, although less convincing, for vitamin D deficiency and the risk of multiple sclerosis (Munger et al., 2004, 2006).

A major boost to the hypothesis came with the demonstration of the effects of vitamin D on immune function. D3 is hydroxylated to the major circulating form, 25(OH)D3, and then, through a second hydroxylase, to the biologically active 1,25(OH)2D3. Catabolism involves a third hydroxylase. 1,25(OH)2D3 exerts its effects through the vitamin D receptor, which acts as a ligand-activated transcription factor by binding to vitamin D response elements in the promoter regions of vitamin D responsive genes. The vitamin D receptor is expressed on antigen-presenting cells and activated lymphocytes and extensive studies support a role for 1,25(OH)2D3 in diverting the immune response away from a pro-inflammatory response, possibly through the enhancement of regulatory T-cell (Treg) activity and secretion of anti-inflammatory cytokines including interleukin 10 (IL-10) (recently reviewed by Smolders et al., 2008). Experimental autoimmune encephalomyelitis, a model for autoimmune demyelination in the central nervous system, is prevented by treatment with 1,25(OH)2D3 prior to immunization with myelin peptides and ameliorated when given after disease onset. There is conflicting evidence on the cellular mechanisms; vitamin D is not effective in IL-10 knockout mice (Spach et al., 2006).

Genetic variants exist in the genes encoding the vitamin D receptor and the major vitamin D hydroxylases (CYP2R1, CYP27B1, CYP24) but convincing data for the association with multiple sclerosis have not been published. The results of the Wellcome Trust genome-wide association scan involving over 11,000 people with multiple sclerosis, due to be released soon, will address this. One definitive finding in multiple sclerosis research is the genetic association with HLA-DRB1*15 in patients of northern European origin. The recent finding of a highly conserved vitamin D receptor response element in the promoter region of the HLA-DRB1*1501 gene has raised the possibility of a functional interaction between vitamin D and the biologic effect of the strongest genetic association in multiple sclerosis (Ramagopalan et al., 2009).

In this issue of Brain, Correale and colleagues propose two new pieces to add to the puzzle. By measuring serum levels of 25 (OH)D3 and 1,25 (OH)2D3 in 58 patients with relapsing–remitting multiple sclerosis in remission, 34 patients studied during a relapse, 40 patients with primary progressive multiple sclerosis and 60 normal controls, they report significant differences (P < 1 × 10-5) between patients with relapsing–remitting multiple sclerosis and healthy controls and between the two relapsing–remitting groups. No differences in the levels were found between primary progressive multiple sclerosis and controls. The authors propose that these differences suggest that vitamin D-dependent T-cell regulation may play an important role in the cause and ongoing activity of multiple sclerosis. To explore this, they studied the
immunoregulatory effects of vitamin D on CD4+ T cells in vitro, the results of which support and extend previous studies suggesting that vitamin D down-regulates autoimmune activity through inhibition of CD4+ T-cell proliferation and enhancement of cells secreting IL-10, whilst inhibiting those producing IL-6 and IL-17 and the induction of CD4+CD25+FoxP3+ Treg through increased expression of indoleamine dioxygenase. Their studies involve the use of well-validated in vitro models of T-cell function.

Do these two pieces fit together to support the authors’ conclusion that there may be a causal relationship between low serum vitamin D levels and disease activity in relapsing–remitting multiple sclerosis (through a process not evident in primary progressive cases) and that correction of the deficiency may control disease relapse? This would appear to be unlikely. Whilst statistically highly significant, the differences in serum vitamin D levels between each group are modest: for 25(OH)D3, mean levels were 38.5, 47.3 and 61.2 ng/ml for patients in relapse, remission and controls, respectively, with figures of 23.0, 29.2 and 35.1 pg/ml for 1,25(OH)2D3. In contrast, the concentrations of 1,25(OH)2D3 used in the in vitro assays were 80- to 500-fold higher than levels found in healthy individuals. If the serum level data, however, can be replicated by others and controlled for the confounding effect of disability on sunlight exposure (van der Mei et al., 2007), the implication is that the case for a clinical trial would be strengthened. To date, emphasis has been on effects in childhood for which a public health intervention would be a major undertaking and outcomes many years away.

Overall, the association between reduced exposure to solar radiation and multiple sclerosis is well supported; but a causal link through the immunologic effects of relative vitamin D deficiency, whilst enjoying some biological plausibility, remains an interesting hypothesis that still has many pieces missing from the puzzle and awaits definitive data.

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References


