Commentary

Vitamin D and multiple sclerosis hospital admissions in Scotland

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It is now acknowledged that seasonality is a main feature of the complex neurological disorder multiple sclerosis (MS). Having a spring birthday and being exposed to low levels of sunshine significantly increase the risk of MS later in life.1,2 Although global environment is dominated by seasonality, the observation that vitamin D status is inversely associated with risk of MS later in life and that vitamin D regulates the expression of a large number of MS associated genes, strongly indicate that ultra-violet (UV) light exposure and consequent effects on vitamin D production are involved in MS etiology.3,4 Intriguingly this essential hormone appears to also play an important role in influencing MS disease course. Studies have shown an inverse association between 25-hydroxyvitamin D (25-OH-D) levels and clinical MS severity and relapse rate.5 Furthermore, in a recent prospective investigation of a large cohort of MS patients, vitamin D status inversely correlated with relapses over the subsequent 6 months.6 Similar findings have also been reported in a large study of pediatric MS patients.7

To provide further support to the disease course modulating role of vitamin D, we investigated the association between MS activity and vitamin D status in the Scottish population. We recently reported that MS hospital admissions in Scotland follow a seasonal distribution by comparing the monthly occurrence of hospital admissions for which MS was the principal diagnosis (n = 7098) with all other emergency admissions (n = 6 243 690) between 1997 and 2009.8 Information on mean 25-OH-D levels were obtained from a previously described large cohort of Scottish adult individuals (n = 712).9 Levels during the month of hospital admission as well as 1, 2 and 3 months before admission and average levels over the previous 3 months were calculated for each month. These continuous variables were tested for correlation with risk of MS vs. non-MS admission using the Spearman correlation coefficient. When monthly 25-OH-D levels were taken individually, only 2 and 3 months lagged levels were inversely and equally associated with risk of admission (Spearman’s rho = −0.587, P = 0.045). However, the strongest correlation was observed for average vitamin D status between the month of admission and the 3 months before the admission (Spearman’s rho = −0.657, P = 0.02) (Figure 1).
These results indicate that low 25-OH-D levels may be triggering the onset of relapses manifesting even 3 months later. However, these findings should be interpreted with caution as patients may well wait weeks and the worsening of symptoms before going to hospital. As a consequence, emergency admissions do not necessarily coincide with onset of relapses. Furthermore, we are not aware of any disease modifying therapy that patients may be taking and indeed what acute admissions with a reported diagnosis of MS represent. In addition we must remember that general population vitamin D status only represents an indirect indicator of individual patient status. While we acknowledge that these factors may be confounding our results, the large sample size and now strong a priori evidence for a role of vitamin D in MS make the risk of a spurious association less likely.

In biological terms vitamin D is likely to directly influence the immunological response driving the onset of MS relapses. Notably, not only the expression of many MS associated genes such as HLA-DRB1, CLEC16A, IRF8, CYP27B1, CD40, TNFRSF1A and MPHOSPH9 appear to be regulated by vitamin D, but also Th1, Th17 and Treg differentiation, activity and proliferation and dendritic cell-mediated antigen presentation are influenced by this exceptionally pleiotropic hormone.\(^4\)\(^,\)\(^10\)\(^,\)\(^11\) This is especially relevant as a correct balance between Th17 and Treg subsets is thought to play an important role in determining MS activity.\(^12\)\(^,\)\(^13\) Furthermore, vitamin D has been shown to protect against upper respiratory tract infections which have also been associated with onset of MS relapses.\(^14\)\(^,\)\(^15\) Therefore we believe that the effect of vitamin D deficiency may also be mediated by an increased susceptibility to infections.

These considerations are extremely relevant as they highlight the need for well-powered randomized placebo-controlled clinical trials which would firmly prove or disprove the potential therapeutic effect of vitamin D in MS. Notably, two small vitamin D\(_3\) clinical trials have demonstrated that high doses (up to 40 000 IU/day) of vitamin D\(_3\) are safe and appear to decrease frequency of relapses, T cell proliferation and the mean number of Gadolinium-enhancing lesions on MRI.\(^16\)\(^,\)\(^17\) Given the potential benefit that modulating the immune response using vitamin D in MS patients can have, we think that further studies are strongly warranted.

**Funding**

This work was supported by the Wellcome Trust [075491/Z/04] and by a research fellowship FISM-Fondazione Italiana Sclerosi Multipla-Cod: 2010/B/5.

**Conflict of interest:** None declared.

**References**


