Vitamin D, past sun exposure & skin phenotype in risk of central nervous system demyelination

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Abstract Latitudinal gradients in multiple sclerosis are well-described in both northern and southern hemispheres. Previous studies have suggested that sun exposure and/or vitamin D may provide an explanation for the latitudinal gradient. The Ausimmune Study was a multi-centre case control study specifically designed to address this question. Between 1 Nov 2003 and 31 Dec 2006, the study recruited 282 cases, aged 18-59 years, with a first clinical diagnosis of central nervous system demyelination (FCD) from four regions of Australia, spanning latitudes of 27°S to 43°S. Controls were matched on age, sex and study region to cases. Data collected included subjective and objective measures of skin type and past sun exposure and vitamin D status (serum 25-hydroxyvitamin D, 25(OH)D). There was a strong latitudinal gradient in FCD incidence. In case-control analyses higher levels of past sun exposure or 25(OH)D were associated with lower risk of FCD; these factors in combination explained 22% of the observed latitudinal gradient in FCD incidence.

Background

Multiple sclerosis is a T-cell mediated disease characterized by immune destruction of myelin sheaths in the central nervous system. One of the most striking features of the epidemiology of multiple sclerosis (MS) is a latitudinal gradient in occurrence (McLeod, Hammond et al. 1994). Previous research has suggested that higher levels of sun exposure (van der Mei, Ponsonby et al. 2003) and/or vitamin D (Munger, Levin et al. 2006) may decrease the risk of multiple sclerosis, with support from both experimental (Cantorna, Hayes et al. 1996) and epidemiological studies (van der Mei, Ponsonby et al. 2001; Munger, Zhang et al. 2004; Munger, Levin et al. 2006). In addition, MS incidence appears to be increasing and the latitude gradient to be decreasing (Ascherio and Munger 2007). If low levels of sun exposure or vitamin D were important for MS onset, increasing incidence would be consistent with lower levels of sun exposure and higher levels of sun protection associated with strong public health programs for sun protection.

Previous work examining latitudinal gradients (McLeod, Hammond et al. 1994), or MS risk in relation to sun exposure and/or vitamin D, has used prevalent cases (van der Mei, Ponsonby et al. 2001; Kampman, Wilsgaard et al. 2007), where temporal relationships are not clear and recall bias can impair validity. Two large cohort studies have shown that higher vitamin D intake or serum level (25(OH)D) was associated with decreased MS risk (Munger, Zhang et al. 2004; Munger, Levin et al. 2006), but these studies were unable to concomitantly examine sun exposure or correct for some possible confounders.

In 2003 the Australian Multicentre Study of Environment and Immune Function (the Ausimmune Study) was funded specifically to examine whether there was persistence of a latitudinal incidence gradient in Australia, and then to examine risk in relation to vitamin D and detailed sun exposure measurements.

Methods

Cases: To minimize bias caused by changes in behaviour post-diagnosis, cases (aged 18-59 years) had an incident first clinical diagnosis of central nervous system demyelination (FCD, often precursor to MS onset) within one of four study regions down the Australian seaboard: Brisbane (27° South); Newcastle and surrounds (33° South), Geelong and the Western Districts of Victoria (37° South) and Tasmania (43° South). We aimed for complete case ascertainment in each study region using a two tier notification system involving neurologists, ophthalmologists, general physicians and radiology practices undertaking relevant MRI scans.

Controls: Each case was matched on age, sex and study region to between 1 and 4 controls randomly selected from the Australian Electoral Roll.

Data: Participants completed questionnaires providing data on ancestry, date of arrival in Australia, self-reported sun exposure at different ages in summer and in winter during weekends and holidays (leisure), propensity to burn or tan, use of sun protection, smoking history, exposure to chemicals, skin cancer history and use of vitamin D containing supplements. Each participant also completed a food frequency questionnaire and a calendar recording location of residence and usual leisure sun exposure in summer and winter for every year of life.

Local research officers (LROs) undertook a physical examination, noting eye and natural hair colour, height and weight and presence of solar keratoses and naevi. Skin melanin density was derived from reflectance spectrophotometer readings at 400nm and 420nm for sun exposed (hand, left back shoulder) and unexposed (buttock and upper inner arm) skin, as previously described (Dwyer, Blizzard et al. 2002). LROs made silicone rubber casts of the dorsum of both hands and these were graded using digital photography on a scale of 1 (no sun damage) to 6 (marked sun damage) (Lucas, Ponsonby et al. 2009). We have previously shown that the cast score correlates well with cumulative sun exposure over the lifetime (Lucas, Ponsonby et al. 2009).

Blood was separated and stored at -80°C until study completion. 25(OH)D level was measured by liquid chromatography dual mass spectrometry and DNA was typed for vitamin D binding protein alleles previously noted to alter 25(OH)D levels (Sinotte, Diorio et al. 2009).

Results

91% (n=282) of eligible FCD cases and 60% (n=558) of contacted controls consented to participate in the Ausimmune Study. There was a strong latitudinal incidence gradient increasing from 2.83 per 100,000 in Brisbane (27°S) to 9.90 per 100,000 in Tasmania (43°S), a 3.5 fold increase or 9% per higher degree of latitude (see Fig 1).

Higher past, recent or cumulative self-reported sun exposure were associated with reduced FCD risk, e.g. leisure time sun exposure (age 6y to current) Adjusted Odds Ratio (AOR)=0.69 (95%CI 0.55-0.86) per 1000KJ/m^2 increase in ultraviolet radiation (UVR) dose, with a stronger effect for recent than for early life, sun exposure. Sun-related skin damage as assessed by silicone skin cast score was also associated with decreased risk: AOR=0.43 (95%CI 0.21-0.88) for the highest grade (6), compared to the lowest (2) (see Fig 2). There was an 8% decrease in the odds of being a case per 10nmol/L increase in serum 25(OH)D level (AOR=0.92 (95%CI 0.86-0.98)) and a 34% decrease per 50nmol/L increase (AOR=0.66, 95%CI 0.48-0.91). Further adjustment for skin type and other phenotypic factors did not alter the association. Measures of high dose, intermittent sun exposure, eg. past history of blistering sunburn, were associated with an increased risk of FCD, AOR=1.33 (95%CI 0.93-1.89).

There was some evidence that cases were more likely to start a vitamin D supplement post-diagnosis, but exclusion of those participants who started a supplement after the date of the cases' first episode did not change the findings. There was a gradient of increasing skin fairness with increasing latitude. Differences in skin type, cumulative UVR dose and serum 25(OH)D level accounted for 22% of the higher FCD incidence in the 43°S vs. the 27°S regions.

Conclusion

There is a strong latitudinal gradient in occurrence of a first diagnosis of CNS demyelination in Australia, with some diminution of that reported for prevalent MS in 1994. Lower sun exposure or vitamin D status are associated with increased odds of a FCD. The effects persist after adjustment for skin phenotype and known risk factors for MS. Recent sun exposure appeared to be more important than early-life sun exposure. There was no evidence of a threshold of effect for 25(OH)D level, but rather a continuous decrease in risk across the range of values. Cumulative sun exposure, skin type and 25(OH)D level accounted for only part of the latitudinal FCD incidence gradient in Australia.

Figure 1 Latitudinal variation in FCD incidence in Australia 2003-2006

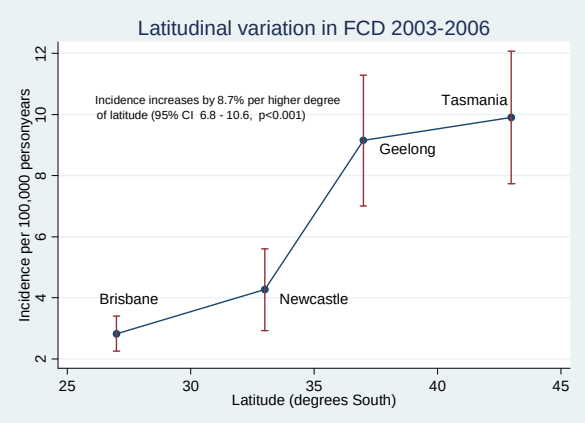
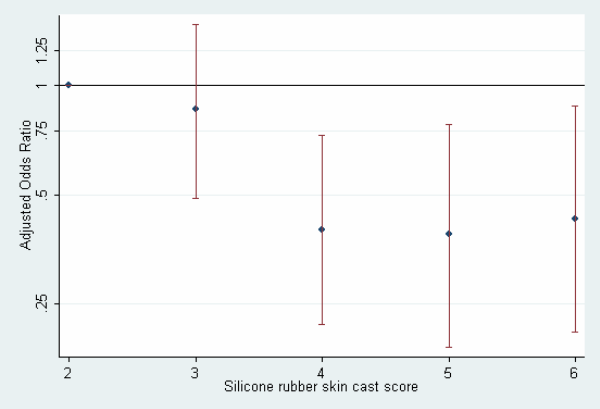


Figure 2 Adjusted odds ratio for FCD status according to skin cast score



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