Sun Exposure, Vitamin D Intake and Progression to Disability among Veterans with Progressive Multiple Sclerosis

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Abstract

Background: Early life events have been suggested to influence multiple sclerosis (MS) susceptibility, and to potentially modulate its clinical course. We assessed vitamin D-related exposures from childhood to disease onset and their associations with MS progression. Methods: Among veterans in the Multiple Sclerosis Surveillance Registry, 219 reported having the progressive form and met the inclusion criteria. Participants reported their past sun exposure, vitamin D-related intake and age at disability milestones using the Patient-Determined Disease Steps (PDDS). The Cox proportional hazards model was used to examine the association between vitamin D-related exposures and time (years) to disability. Results: Low average sun exposure in the fall/winter before disease onset was associated with an increased risk of progressing to a PDDS score of 8 (hazard ratio, HR: 2.13, 95% confidence interval, CI: 1.20–3.78), whereas use of cod liver oil during childhood and adolescence was associated with a reduced risk (HR: 0.44, 95% CI: 0.20–0.96). Conclusions: These results suggest that exposure to vitamin D before MS onset might slow disease-related neurodegeneration and thus delay progression to disability among patients with the progressive subtype.

Introduction

Cumulative evidence supports vitamin D as a strong immune modulator and protective factor against the development of multiple sclerosis (MS) \cite{1, 2}. High sun exposure, cod liver oil intake and fish consumption, especially during childhood and adolescence, were reported to reduce the risk of MS \cite{3–5}.

Little is known about the role of vitamin D in modulating the clinical course of MS. In experimental allergic encephalomyelitis, an animal model of MS, administration of an active form of vitamin D, after immunization but before the appearance of symptoms, was found to prevent MS onset \cite{6–9}, and also to reduce disease severity and prolong survival \cite{7, 8, 10}. In humans, few studies
have shown that very early exposures, probably related to maternal vitamin D level, influence MS risk and possibly its clinical course [11–15]. Whether or not vitamin D levels before MS onset have long-lasting effects on disease progression remains unknown.

In this study we examined the influence of sun exposure and vitamin D intake (diet and supplements) during childhood and early adolescence (6–15 years), and up to symptom onset, on long-term disease disability among veterans with progressive MS.

Methods

The University of Maryland Institutional Review Board and the Veterans Health Administration (VHA) Research and Development Committee at Baltimore VA Medical Center approved this study.

Study Population
The study population was recruited from the VHA Multiple Sclerosis Surveillance Registry, a population-based, self-reported registry of veterans with MS [16]. Questionnaires were mailed to a randomly selected MS veteran cohort to obtain information for both clinical outcomes and epidemiological research purposes as previously reported [15]. Among the 1,328 participants who completed the questionnaire, 245 (18.4%) reported having progressive MS – defined as progressively worsening from symptom onset with or without any recovery from symptoms (remissions) later in the course, including both primary progressive and progressive relapsing MS. We excluded those born and raised outside the USA (n = 12) and those who were younger than 18 years or older than 65 years at symptom onset (n = 13) to limit heterogeneity due to differences in childhood onset, and very late age of MS onset.

Outcome: Time from MS Symptom Onset to Defined Stages of Disability
Participants reported retrospectively their age when they reached disability milestones using the Patient Determined Disability Scale (PDDS), a simple and reproducible assessment of functional disability in MS [17] that correlates well with the Expanded Disability Status Scale [18]. The PDDS primarily evaluates ambulation of MS patients on a scale of 1–9. Only disability stages that each participant has experienced and maintained for at least 6 months were recorded. We selected age at PDDS 8, a stage when a wheelchair or scooter is the main form of mobility, and calculated the time from age of MS symptom onset to disability as our main study outcome.

Ultraviolet Radiation Exposure/Vitamin D Intake
We used participants’ self-reported sun exposure to estimate the cumulative childhood and early adolescence sun exposure as previously reported [15]. The average sun exposure before symptom onset (weeks per year) was calculated by summing up the total hours of sun exposure from the age of 6 years to the age at MS symptom onset and then divided by number of years in that same period. Separate variables of these sun exposure estimates were calculated for fall/winter and spring/summer.

Based on the participants’ self-reported dietary and supplement intake, we derived variables indicating frequency of each food (fish, milk and egg/cheese) and supplement (cod liver oil, vitamin D/calcium and multivitamins) between the ages of 6 and 15 years and up to the age at MS symptom onset.

Other Covariates
Each participant reported age at MS symptom onset, MS subtype, and type of onset symptoms (motor/coordination, sensory, vision, systematic, and bowel and bladder problems) in addition to basic demographics. Diagnosis of mononucleosis before symptom onset (yes/no), smoking status before disease onset and type of skin (using the Fitzpatrick classification [19]) were also documented.

Statistical Analyses
Outcome measure was time from symptom onset to PDDS 8. When the end point was not reported to have been reached by the participants, the time data were right-censored at the date of the survey. Kaplan-Meier analysis was used to examine the distribution and median of each outcome variable.

Log rank tests were used to examine unadjusted associations between time to disability (outcome) and: (1) vitamin D-related exposures before MS onset and (2) a set of potential covariates that could affect outcome or confound the association (i.e. other MS risk factors like gender). Variables having unadjusted associations with time to disability at the less than 0.20 significance level were considered for inclusion in the Cox proportional hazards models. Potential effect modification and collinearity were assessed among variables in these models. Proportional hazard model assumptions were tested for each model. All analyses were performed using SAS version 9.1.

Results

The study sample consisted of 219 veterans with progressive MS. Table 1 shows the demographic and clinical characteristics of study participants, the majority of whom were Caucasians (81%) and males (77%). The mean age at symptom onset was 36.1 years (SD = 10.9). The median age at symptom onset was 36.1 years (SD = 10.9). The median time from symptom onset to PDDS 8 was 27 years (95% confidence interval, CI: 24–33).

All sun exposure variables were first grouped into quartiles, which were examined for their associations with the outcome. Based on the observed trend, these variables were subsequently dichotomized into low versus high sun exposure; for example, average fall/winter sun exposure was compared between ≤1.6 weeks/year (lowest quartile) and >1.6 weeks/year (top 3 quartiles).

The log rank test indicates that participants with low average fall/winter sun exposure before MS onset progressed to PDDS 8 faster than those with higher average
sun exposure ($p = 0.01$; fig. 1a). The median time from disease onset to PDDS 8 was 20 years (95% CI: 16–29) for the former group, compared to 29 years (95% CI: 14–42) for the latter. Neither average spring/summer sun exposure before MS onset nor cumulative exposure between the ages of 6 and 15 were significantly associated with time to PDDS 8.

Cod liver oil intake and fish consumption – between the ages of 6 and 15 years – were associated with time to PDDS 8. Among participants who ever took cod liver oil before MS onset (n = 26), >90% (n = 24) took it between the ages of 6–15, thus, we used the latter as the exposure period. Figure 1b shows that those who ever took cod liver oil reached PDDS 8 later than those who never took it ($p = 0.01$). Subjects, who rarely (less than once a week) ate fish at the age of 6–15, seemed to progress to PDDS 8 faster, although it was not statistically significant ($p = 0.08$). Average fish consumption, vitamin D-related supplements and other dietary intake before MS symptom onset, as well as skin type (known to interfere with sun exposure and vitamin D synthesis), were not associated with time to disability ($p < 0.20$). Covariates, including sensory symptom at onset and diagnosis of mononucleosis, were significantly associated with time to disability ($p < 0.05$) and thus considered for the final model.

We used the Cox proportional hazard model to examine sun exposure and vitamin D intake variables simultaneously, while adjusting for selected covariates (table 2).

We conducted several sensitivity analyses. We compared time to disability from age at diagnosis, instead of from age at symptom onset, and found similar results. Because 14 participants replied ‘unknown’ to the diagno-

### Table 1. Sociodemographic and clinical characteristics of veterans with progressive MS (n = 219)

<table>
<thead>
<tr>
<th>Personal characteristics</th>
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</thead>
<tbody>
<tr>
<td>Mean age ± SD, years</td>
<td>60.9 ± 9.6</td>
<td></td>
</tr>
<tr>
<td>Race, n</td>
<td>178 (81.3)</td>
<td>34 (15.5)</td>
</tr>
<tr>
<td>Sex, n</td>
<td>50 (22.8)</td>
<td>169 (77.2)</td>
</tr>
<tr>
<td>Mean education ± SD, years</td>
<td>14.4 ± 3.0</td>
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</tr>
</tbody>
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**Clinical characteristics**

| Mean age at onset ± SD, years | 36.1 ± 10.9 |
| Mean disease duration ± SD, years | 24.9 ± 12.4 |
| Current PDDS stage ± SD | 6.8 ± 1.6 |
| Time from onset to PDDS 8$^a$ | 27 [24–33] |
| DX of mononucleosis, n | 33 (15.4) |
| Yes | 166 (77.6) |
| No | 15 (7.0) |

$^a$ Kaplan-Meier estimates of time to PDDS 8 (median time and 95% CI in brackets indicated in years).

### Table 2. Adjusted proportional hazard ratios of different factors associated with time from disease symptom onset to PDDS 8 among veterans with progressive MS (n = 151)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Age at symptom onset</td>
<td>1.03 (1.0–1.06)</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender Male vs. female (reference)</td>
<td>1.19 (0.62–2.23)</td>
<td>0.60</td>
</tr>
<tr>
<td>Average fall/winter sun exposure before MS onset Low vs. high (reference)</td>
<td>2.13 (1.20–3.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>DX of mononucleosis before MS onset Yes vs. no (reference)$^a$</td>
<td>2.65 (1.33–5.27)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cod liver oil intake at ages 6–15 years Ever vs. never (reference)</td>
<td>0.44 (0.20–0.96)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fish consumption at ages 6–15 years Sometimes vs. rarely (reference)</td>
<td>0.79 (0.45–1.41)</td>
<td>0.43</td>
</tr>
<tr>
<td>Often/very often vs. rarely (reference)</td>
<td>0.58 (0.31–1.08)</td>
<td>0.09</td>
</tr>
<tr>
<td>Sensory symptom at onset Present vs. absent (reference)</td>
<td>0.56 (0.34–0.91)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Only 151 out of 219 veterans with progressive MS were included in the model due to missing values. Figures in parentheses indicate 95% CI. DX = Diagnosis before onset of MS.

$^a$ 14 veterans reported ‘unknown’ for this variable.
sis of mononucleosis, we alternatively assigned ‘yes’ or ‘no’ to the unknowns and refit the model: no significant change in the results for any of the variables in the model. Furthermore, we examined demographic and clinical characteristics of those who had completed exposure and outcome variables (n = 151) and compared them to those with missing data (n = 68); we found no significant differences.

**Discussion**

We investigated the dual influence of sun exposure and vitamin D-related intakes before MS onset on disease progression. We found that among veterans with progressive MS, low average fall/winter sun exposure before disease onset was associated with an increased risk of disability, whereas cod liver oil intake and fish consumption during childhood and adolescence were associated with a lower risk.

Exposures early in life, probably related to maternal levels of vitamin D, were found to have long-lasting effects on the clinical course of MS [11–15]. These findings led investigators to postulate that ultraviolet radiation and vitamin D exert their beneficial effects by modulating the development of the nervous system and/or immune system in the fetus. Our data extend the previous findings and suggest that vitamin D-related exposures from childhood to the age at MS onset might also affect long-term disease outcomes among patients with progressive MS.

One previous study investigated the association between disability in MS and ultraviolet radiation exposures during childhood (0–16 years) and adult life (17–40 years) among 448 Caucasian patients and did not find any significant effects [20]. The discrepancy in the results between that study and ours may be due to methodological differences including choice of the outcomes (Expanded Disability Status Scale vs. PDDS), exposure measurements (cumulative sun exposure in specified age periods vs. average sun exposure up to the age at symptom onset) and statistical approaches (logistic regression vs. survival analysis). Moreover, the previous study did not control for MS subtype, and it is likely that the majority of the subjects in that study had relapsing MS. In our original study’s cohort, the majority of patients with relapsing MS have not reached the disability level to the studied end points, and we did not find significant associations between sun exposure and disability (data not shown). Because patients with relapsing MS represent a highly heterogeneous group with respect to clinical course and prognosis, it is possible that the protective effect of sun exposure and vitamin D intake is diluted and difficult to detect among these patients. The effects are also potentially subject to other confounding factors such as use of disease-modifying therapy.
There is evidence indicating that vitamin D has strong neuroprotective effects, and thus could potentially be used in the treatment of some neurodegenerative diseases [21]. In MS, neurodegenerative changes are thought to be the major causes of its progression and disability accumulation [22], although autoimmunity and inflammation drive the development of the disease and its early activities. Therefore, in conjunction with our present finding among subjects with progressive MS, it is plausible that the neuroprotective effect of vitamin D could delay disease-related degeneration in the nervous system and thus influence long-term disability in MS.

We found that patients with a history of mononucleosis before their disease onset had a higher risk of progressing to disability, compared to those with a negative history. Epstein-Barr virus has been identified as a risk factor for MS [23]. Infectious mononucleosis, an indicator of late-age Epstein-Barr virus infection, was also associated with an increased risk of MS [24]. However, the role of this infectious agent in disease progression is largely unknown, although a few studies have suggested that viral or bacterial infections might trigger exacerbations among patients with relapsing-remitting MS [25, 26]. Additional studies are required to investigate the potential role of infections, either chronic or recurrent, in long-term MS disability.

Identifying reliable MS prognostic factors has been challenging, and very few have been consistently reported across studies. We found that younger age at onset, previously considered as a good prognostic factor for MS [27], was associated with longer time to disability. However, several studies have found that despite longer time to disability stages, individuals with younger age at onset reached disability at a younger age [28, 29], results that are supported by our finding when we used age at disability stage as the study outcome (data not shown). Our finding that presence of sensory symptoms at MS onset was associated with better prognosis is consistent with a recent study showing the existence of sensory symptoms at onset as a main factor for favorable prognosis among patients with primary progressive MS [28].

Even though we have identified some vitamin D-related exposures associated with disease progression among patients with progressive MS, these results are preliminary and should be interpreted with caution, considering the relatively small number of patients in the final analysis and limitations associated with the nature of the study design. Replication by future studies is required to confirm these findings. Limitations in the present study are potential recall bias and measurement errors related to self-reported data. Although we used a modified version of a questionnaire that was previously shown to be a fairly reliable means to record past sun exposure among MS and other disease populations [3, 30], possible misclassification of the sun exposure and other variables cannot be excluded. A cross-sectional study design is subject to a potential birth cohort effect. Participants who belong to an older birth cohort might have different exposure patterns regarding vitamin D intake and sun exposure compared to those in younger cohorts. In our regression model, we adjusted for age at MS onset and thus indirectly controlled for potential birth cohort effect. To address the latter more directly, a separate regression model was fitted controlling for the participant’s current age (instead of age at onset). The results showed that current age was not significantly associated with time to disability (p = 0.11) and the effects of all exposures remained the same. Furthermore, despite the fact that PDDS is a useful tool for the assessment of long-term disability, it is highly weighted by ambulation functions and does not consider other signs and symptoms resulting from disease progression, such as cognitive dysfunction.

In summary, the current study suggests protective effects of vitamin D-related exposures before MS onset on disability among veterans with progressive MS. It is possible that, through its immunomodulatory and/or neuroprotective functions, vitamin D slows disease-related neurodegeneration, which may have implications for disease prevention among populations at high risk for MS. These findings, if proven, would have clinical implications in terms of MS prevention among populations at risk as well as disease intervention. Only a randomized trial would provide more definitive answers about the effects of vitamin D on the progression of MS.

Acknowledgement

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