

## ONLINE FIRST

# Low Serum Vitamin D Levels and Recurrent Inflammatory Spinal Cord Disease

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**Background:** Low 25-hydroxyvitamin D levels have been associated with a higher risk of developing multiple sclerosis and increased relapse rates in patients with multiple sclerosis. As a sterol hormone involved in multiple immunologic pathways, vitamin D may play a role in preventing monophasic immune-mediated central nervous system attacks from developing into recurrent disease.

**Objective:** To investigate the association between low serum vitamin D levels and recurrent spinal cord disease.

**Design, Setting, and Patients:** We performed a retrospective analysis at Johns Hopkins Transverse Myelitis Center, Baltimore, Maryland, evaluating 25-hydroxyvitamin D levels in 77 patients with monophasic and recurrent inflammatory diseases of the spinal cord.

**Main Outcome Measure:** Levels of 25-hydroxyvitamin D.

**Results:** Vitamin D levels are significantly lower in patients who developed recurrent spinal cord disease, adjusting for season, age, sex, and race.

**Conclusions:** This study provides a basis for a prospective trial of measuring 25-hydroxyvitamin D levels in these patient populations and assessing the influence of vitamin D supplementation on the frequency of relapses in those with recurrent inflammatory spinal cord disease.

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**I**N RECENT YEARS, LOW LEVELS OF VITAMIN D have been linked to a variety of autoimmune conditions including multiple sclerosis (MS).<sup>1</sup> Studies have shown that low levels of vitamin D increase the risk of developing MS and are associated with an increase in the relapse rate in patients with known MS.<sup>2,3</sup> However, the importance of vitamin D in monophasic or recurrent non-MS spinal cord diseases including transverse myelitis (TM) and neuromyelitis optica (NMO) is unknown. Based on in vivo and in vitro studies, there is evidence that vitamin D deficiency may be a component of the pathobiology that leads to recurrent autoimmune attacks.<sup>4-7</sup>

Idiopathic TM (ITM) is monophasic in nature and characterized by focal inflammation within the spinal cord. Approximately 75% to 90% of patients with TM experience monophasic disease and have no evidence for recurrent disease or multisystemic involvement.<sup>8</sup> Patients are considered to be at greater risk for recurrent central nervous system (CNS) attacks if they have multifocal lesions within their spinal cord or demyelinating lesions within

their brain, oligoclonal bands in their cerebrospinal fluid, a coexisting rheumatologic disorder, or serum autoantibodies (most notably SS-A or NMO-IgG).<sup>9,10</sup> Other risk factors for the development of recurrent disease, such as low vitamin D levels, have not been widely explored.

Neuromyelitis optica is considered to be a recurrent CNS disorder characterized by longitudinally extensive TM plus optic neuritis. Most patients with NMO have recurrent rather than monophasic disease.<sup>10</sup> Neuromyelitis optica is associated with a highly specific antibody marker, NMO-IgG, that targets the water channel aquaporin 4.<sup>10</sup> Despite a fair sensitivity of 58%, NMO seropositivity is highly specific for NMO and NMO spectrum disorders, with more than 99% of seropositive patients with spinal cord or optic nerve disease developing NMO.<sup>11</sup>

It is not well understood why some patients experience a monophasic CNS inflammatory attack while others have recurrent disease. Previous studies have demonstrated that patients with both monophasic and recurrent transverse myelitis have elevated levels of serum

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**Table. Patient Characteristics**

| Characteristic   | No. (%)              |                     |
|--|----------------------|---------------------|
|  | Monophasic<br>(n=44) | Recurrent<br>(n=33) |
| Female   | 24 (55)              | 24 (73)             |
| Age, median, y   | 46.5                 | 48                  |
| Race   |                      |                     |
| White  | 40 (91)              | 14 (42)             |
| African American   | 2 (5)                | 16 (48)             |
| Other  | 2 (5)                | 3 (9)               |
| Mobility   |                      |                     |
| Unassisted   | 26 (59)              | 16 (48)             |
| Unilateral assistance  | 2 (5)                | 4 (12)              |
| Bilateral assistance   | 4 (9)                | 4 (12)              |
| Wheelchair   | 12 (27)              | 9 (27)              |
| Season   |                      |                     |
| Fall <sup>a</sup>  | 11 (24)              | 7 (21)              |
| Winter <sup>b</sup>  | 6 (13)               | 8 (24)              |
| Spring <sup>c</sup>  | 8 (17)               | 6 (18)              |
| Summer <sup>d</sup>  | 19 (41)              | 12 (36)             |
| NMO-IgG  |                      |                     |
| Seropositive   | 0                    | 20 (61)             |
| Seronegative   | 44 (100)             | 13 (39)             |
| Time from onset of disease<br>to vitamin D draw,<br>median/mean, y | 1/3.1                | 1.5/4.0             |

<sup>a</sup>September through November.

<sup>b</sup>December through February.

<sup>c</sup>March through May.

<sup>d</sup>June through August.

and/or cerebrospinal fluid interleukin 6 (IL-6), IL-8, and IL-17,<sup>12-14</sup> cytokines that are important in both triggering an inflammatory attack as well as suppressing immune responses. Interestingly, the inflammatory milieu of CNS disorders appears to be altered in the presence of vitamin D.<sup>15,16</sup> Vitamin D supplementation has been linked to reductions in IL-6 and IL-1 $\beta$  production in vivo<sup>17,18</sup> as well as interferon  $\gamma$  and IL-17 in vitro.<sup>19</sup> The active metabolites of vitamin D can suppress Th17-mediated autoimmunity,<sup>20</sup> and elevated levels of vitamin D have also been found to augment T-cell regulatory cell populations, providing a possible mechanism for preventing autoimmunity.<sup>21</sup> While there are likely many factors that differentiate patients with monophasic vs recurrent CNS inflammatory disease, vitamin D levels may be one factor. We hypothesized that vitamin D levels are lower in patients with recurrent inflammatory spinal cord disorders as compared with those with monophasic ITM. To our knowledge, this is the first study demonstrating that lower vitamin D levels correlate with recurrent spinal cord diseases such as NMO and NMO spectrum disorders as compared with monophasic spinal cord diseases like ITM.

## METHODS

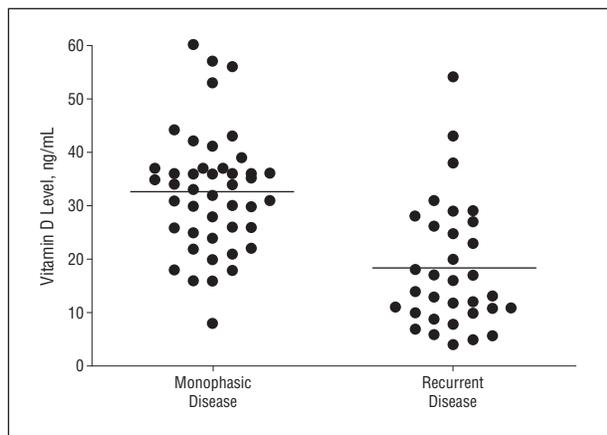
A retrospective record review was performed for patients who had their total 25-hydroxyvitamin D levels drawn for clinical purposes at the Johns Hopkins Transverse Myelitis Center and NMO Clinic who have been seen at the Johns Hopkins Transverse Myelitis Center within the last 6 years. This review was

approved by the Johns Hopkins Institutional Review Board. To ensure that all patients were included, the Johns Hopkins Transverse Myelitis Center database log was used and cross-referenced with everyone for whom the NMO-IgG laboratory test was ordered. Additionally, race, sex, zip code at the time of draw, age at draw, season at draw, diagnosis, NMO-IgG status, elapsed time from disease onset to laboratory draw, and mobility status at draw (unassisted, unilateral assistance, bilateral assistance, or wheelchair) were recorded. Race was qualified as white, African American, or other and was based on self-report. Patients were included if their 25-hydroxyvitamin D level was measured outside the Hopkins system. We obtained information about the assay used at each laboratory except for 1 sample in the recurrent TM group that was processed at an outside laboratory in 1999. All other vitamin D levels were drawn between June 14, 2005, and January 12, 2011, and processed at Johns Hopkins, Quest, or Labcorp by liquid chromatography, immunochemiluminometric assay, and chemiluminescence assay. There was no significant difference in the average vitamin D level in each group when divided by assay. Patients were excluded if their daily supplemental intake of vitamin D exceeded 800 IU at the time of blood draw. If more than 1 vitamin D level was drawn, the earliest laboratory value logged in the patient record was used. All laboratory values were drawn after or during the first clinical neurological event as shown in the **Table**. Patients were excluded if the time from the first clinical symptom to laboratory draw exceeded 25 years.

Patients were divided into either a monophasic ITM group or a recurrent TM/NMO/NMO spectrum disorders group. For those in the monophasic ITM group, an extensive workup for an underlying causative agent for the TM had been performed as part of their clinical care. Patients were excluded from this group if they had evidence of prior CNS inflammation or demyelination, an infectious cause, or a diagnosis or evidence of MS or rheumatologic disease. To be considered monophasic for this study, only patients with at least 1 year of follow-up from the time of their inflammatory event were included (mean follow-up, 4.9 years; range, 1-22 years), and they must have been disease free without immunomodulatory or immunosuppressive treatment during this time. Patients with recurrent TM/NMO/NMO spectrum disorders were included even if a concomitant rheumatologic disease was present, including Sjögren syndrome and systemic lupus erythematosus (4 patients had systemic lupus erythematosus and 1 patient had Sjögren syndrome).

Statistical analyses were completed using Stata version 10 statistical software (StataCorp LP, College Station, Texas). Reported *P* values are 2-tailed and statistically significant if *P* < .05. Medians were compared by Mann-Whitney rank sum test. Vitamin D levels between the groups (ie, ITM vs recurrent TM) were assessed using linear regression analysis.

In this model, we adjusted for differences in age, race, sex, and season at the time of vitamin D level draw. Disability and age have been shown to be inversely associated with vitamin D status in MS.<sup>3,22</sup> Therefore, a comparison of vitamin D level and need for varying assistive devices and a correlation to address age and vitamin D status were done. Because race has also been associated with vitamin D status such that African American individuals have lower levels than non-Hispanic white individuals,<sup>23</sup> we performed a separate analysis where the African American cohort was removed and only the remaining patients were evaluated. Also, a correlation was done to explore the relationship between vitamin D levels and the elapsed time from the first clinical event to laboratory draw. Owing to the rarity of the diseases in both groups and sample size, we could not stratify patients by latitude as has been done in MS studies.<sup>24</sup>



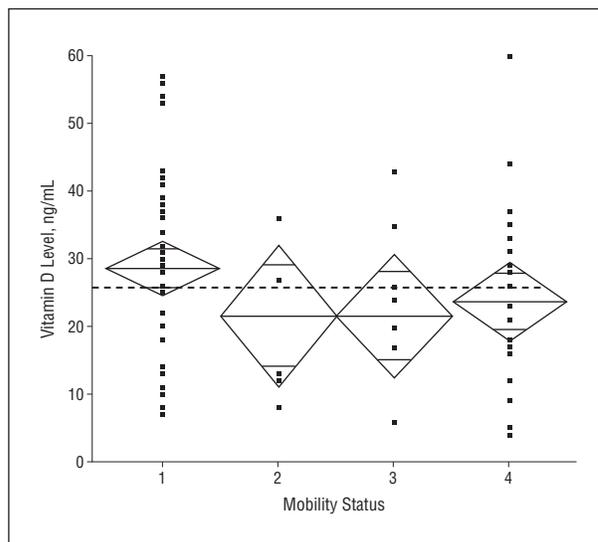
**Figure 1.** Total 25-hydroxyvitamin D levels were 10 ng/mL lower in the recurrent group compared with monophasic idiopathic transverse myelitis ( $P = .002$ ). To convert vitamin D to nanomoles per liter, multiply by 2.496.

## RESULTS

There were a total of 44 patients in the ITM group and 33 patients in the recurrent TM group. The 2 groups in this study were similar in several demographic features (Table). The median age was 46.5 years for the monophasic group (range, 1-78 years) and 48 years for the recurrent TM group (range, 14-86 years) ( $P = .36$ ). The need for assistive devices was similar between the groups, as was the season in which the vitamin D level was drawn. The mean (SD) times from the first clinical event to the time of blood draw were 3.1 (4.3) years (range, 0-21 years) and 4.0 (5.0) years (range, 0-18 years) in the monophasic and recurrent cohorts, respectively. The majority of patients (35 patients [80%] in the ITM group and 24 patients [74%] in the recurrent TM group) were clustered in the mid-Atlantic region of the United States.

Total 25-hydroxyvitamin D levels were significantly lower in patients with recurrent TM as compared with patients with ITM (**Figure 1**). Prior to adjusting for demographic differences, the mean (SD) 25-hydroxyvitamin D levels were 33 (11.1) ng/mL (range, 8-60 ng/mL; to convert to nanomoles per liter, multiply by 2.496) in the ITM group and 18 (11.8) ng/mL (range, 4-54 ng/mL) in the recurrent group. The Johns Hopkins Hospital laboratory defines vitamin D deficiency as being lower than 20 ng/mL and optimal levels as higher than 30 ng/mL. After adjusting for age, race, sex, and season, the vitamin D level in patients with recurrent TM/NMO/NMO spectrum disorders was a mean (SE) of 10 (3.1) ng/mL lower than in patients with ITM ( $P = .002$ ; 95% CI, 16.3-3.9). The mean (SD) 25-hydroxyvitamin D level for the rheumatologic disease subgroup within the recurrent group was 20 (13.8) ng/mL (range, 6-38 ng/mL).

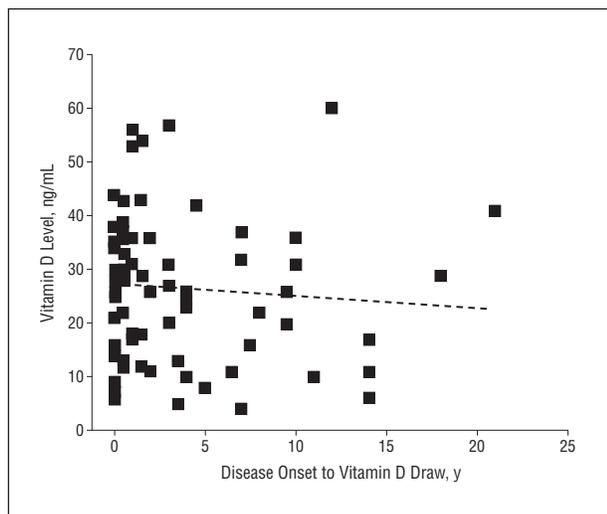
We found 2 major demographic differences between the groups. The first is that females accounted for 24 cases (73%) of the recurrent TM group, whereas they made up just more than half (24 females [55%]) of those with monophasic disease. The 3:1 female to male ratio in the recurrent disease group is similar to that of other recurrent autoimmune disorders.<sup>25</sup> The second major difference is that African American patients composed half of the recurrent TM group, and



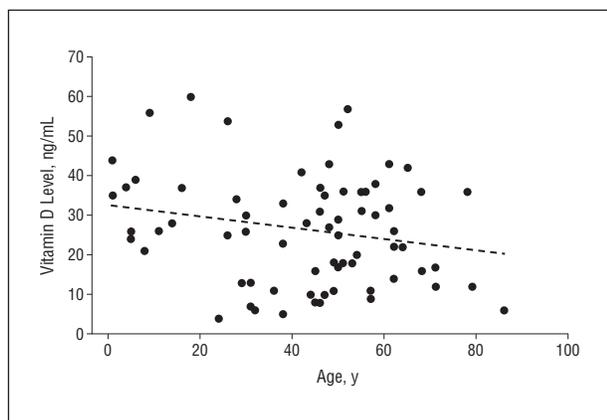
**Figure 2.** Need for assistive devices does not significantly impact vitamin D levels ( $P = .30$ ). 1 indicates unassisted; 2, unilateral assistance; 3, bilateral assistance; and 4, wheelchair. For each category, the diamond represents the 95% CI and lines within the diamonds represent the 75th percentile, mean, and 25th percentile from top to bottom, respectively. To convert vitamin D to nanomoles per liter, multiply by 2.496.

only 2 were in the ITM group. In total, 16 of the 18 African American patients (89%) in this study developed recurrent disease compared with 14 of the 54 white patients (26%). This finding is also consistent with other autoimmune diseases in which minority races/ethnicities make up a disproportionate number of total cases.<sup>26</sup> These factors are statistically accounted for in our analysis. Given that race is a well-known confounding factor affecting vitamin D levels and that there is a markedly disproportionate number of African American patients in the recurrent TM group, a separate analysis was performed after excluding the African American patients from each group to determine whether race alone can account for the differences in vitamin D levels. Even with excluding African American patients, there was a significant difference between vitamin D levels of the 2 groups such that the vitamin D level was a mean (SE) of 9 (3.5) ng/mL lower in the recurrent TM group as compared with the ITM group ( $P = .01$ ; 95% CI, 1.9-15.9).

Mobility status and age are cofactors that have been shown to be inversely associated with vitamin D levels in patients with MS and healthy individuals. We computed a 4-level, 1-way analysis of variance on mobility or disability status as measured by the need for assistive devices (unassisted, unilateral assistance, bilateral assistance, wheelchair) at the time of blood draw and vitamin D level (**Figure 2**). The mean vitamin D level across each disability group was not significantly different ( $P = .30$ ). We also found only a slight decrease in vitamin D levels as the time increased from disease onset to blood draw (**Figure 3**) ( $P = .51$ ;  $r = 0.005$ ). However, there is a stronger trend toward decreasing vitamin D levels with age in the combined patient populations of inflammatory spinal cord disease ( $P = .06$ ;  $r = 0.044$ ) (**Figure 4**). Owing to the potential confounding effect on vitamin D levels, we accounted for age in our regression analysis.



**Figure 3.** Length of time between disease onset and blood draw does not correlate with decreasing vitamin D levels ( $P=.51$ ;  $r=0.005$ ). To convert vitamin D to nanomoles per liter, multiply by 2.496.



**Figure 4.** Although there was a trend toward an inverse correlation between age and vitamin D levels with the combined spinal cord disease population, this was not significant ( $P=.06$ ;  $r=0.044$ ). To convert vitamin D to nanomoles per liter, multiply by 2.496.

## COMMENT

Our findings suggest that there may be an association between lower total 25-hydroxyvitamin D levels in patients with recurrent TM/NMO/NMO spectrum disorders as compared with their counterparts with monophasic disease. This is consistent with other recurrent autoimmune conditions and points to a common link between low vitamin D levels and immunologic dysregulation. Given that vitamin D deficiency may play a role in the development of MS and risk of relapses in those with known MS, this study adds to a growing body of evidence that inadequate vitamin D levels may affect the development and recurrence of other immune-mediated CNS disorders like recurrent TM and NMO.

A limitation of this study is that it is retrospective. As a result, some covariates of vitamin D were not accounted for, including potential differential significance of D<sub>3</sub> vs D<sub>2</sub> forms of vitamin D, body mass index, daily sun exposure, and latitude during childhood.<sup>27-30</sup>

Another limitation to this study is that vitamin D levels were not drawn at the same time in the disease state for each patient. In our patient population, vitamin D levels did not significantly fluctuate during the disease course. One-third of the total cohort with recurrent TM had vitamin D levels drawn within 6 months of disease onset, and these did not differ from the total cohort's mean vitamin D level that spanned many years (data not shown). Because the cause and effect of low vitamin D levels on relapses in this patient population are not well understood, we do not know whether the disorder can actually influence vitamin D levels over time or whether perhaps vitamin D levels can influence the disorder. Furthermore, some patients had levels drawn during acute inflammatory events, whereas others were drawn during follow-up clinic visits; again, we do not know the impact this may have in terms of influencing fluctuations in vitamin D levels in this patient population.

Future prospective studies are needed to further assess the relationship between vitamin D and recurrent TM/NMO/NMO spectrum disorders and to examine the influence of vitamin D supplementation on the frequency of relapses in these patients.

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