Objectives: To assess the association between vitamin D [25(OH)D] and irreversible brain tissue damage characterized by the occurrence of persistent T2-hypointense (permanent black holes [PBHs]) in patients with clinically isolated syndrome (CIS) who were followed for 5 years.

Methods: BENEFIT was a randomized trial comparing early versus delayed interferon beta-1b (IFN-1b) treatment in patients with a first-ever suggestive of MS. Serum 25(OH)D concentrations were measured at baseline, 6, 12, and 24 months. 465 of the 468 patients had at least one 25(OH)D measurement and had lesion follow-up for at least 1 year. We calculated a season-adjusted 25(OH)D and estimated the association between the time-dependent cumulative average of 25(OH)D and the number of new PBHs after 6 months. We modeled lesion counts using negative binomial models and logistic regression models to assess the proportion of lesions evolving into PBHs accounting for intra-patient correlation using generalized estimating equations. We also assessed the association between 25(OH)D and number of lesions of a specific type at initial presentation (nodular Gadolinium [Gd]-enhancement, ring-like Gd-enhancement, T1-isointense, T2 lesions or T1-hypointense lesions). Analyses were adjusted for age, sex, treatment, baseline T2 lesions, and CIS onset type.

Results: A total of 3780 new lesions developed over the 5 year follow-up period with 383 developing into PBHs (10%). Average 25(OH)D levels were significantly inversely correlated with the number of PBHs from the 6-month to five-year MRI; patients with serum 25(OH)D levels ≤50 nmol/L experienced a 55% lower absolute rate of PBHs (95% CI: 0.29 to 0.71; P = 0.006) than those >50 nmol/L. We also observed a marginal association between serum 25(OH)D and the proportion of T2 lesions evolving into PBHs (0.71, 95% CI: 0.50 to 1.01; P = 0.056, comparing patients with ≥50 nmol/L vs those <50 nmol/L). Conclusion: Our results suggest that 25(OH)D levels were associated with lesser accumulation of irreversible brain tissue damage support the importance of adequate vitamin D status in delaying MS progression.

Background

Several previous studies have suggested vitamin D is strongly associated with lower rates of multiple sclerosis (MS) activity characterized by the development of fewer T2 lesions or Gd-enhancing lesion or overall T2 lesion burden. However, for vitamin D on global neurodegenerative processes reflected by grey and white matter volume loss or increases in clinical disability or in MS are more variable. Persistent T1 hypointense lesions (persistent black holes [PBHs]) represent an additional measure to characterize neurodegeneration as PBHs are more strongly associated with clinical disability and brain volume loss than Gd-enhancing or T2 lesions.

Study Population: The Beteferon/Betason in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT) was a randomized trial designed to assess early versus late initiation of interferon beta-1b in patients with clinically isolated syndrome (CIS). Eligible patients presented with a first episode of neuromyelitis optica highly indicative of MS and at least 2 clinically silent lesions on magnetic resonance imaging (MRI) and were randomized IFN-1b (n = 292) or placebo (n = 196) treatment arms. MRI scans were performed at baseline and at three, six, nine, 12 months and annually thereafter. Following the baseline measurement, new Gd-enhancing lesions and new T2 lesions were classified by mutually exclusive subtypes (nodular Gd-enhancement on enhanced T1-weighted images; ring-like Gd-enhancement on enhanced T1-weighted images; isointense T2 lesion on enhanced T1-weighted images or hypointense T2 lesion on T1-weighted images). We defined a lesion as irreversible if it remained visually detectable on T2-weighted images for at least 1 year, if surrounded by normal or hyperintense grey matter and considered a lesion to be a PBH if the hypointensity was confirmed at the last available scan (where each potential hypointensity needed to be observed for a period of at least 1 year).

Measurement of 25(OH)D: Serum samples were collected at baseline and at three, six, nine, 12 months and annually thereafter. Serum 25(OH)D levels were measured using enzyme-linked immunosorbent assay (ELISA) at baseline and at 6, 12, and 24 months. Serum 25(OH)D values to remove extraneous seasonal variation and to obtain an estimate of an individual’s long term vitamin D status. Assessment of PBHs: MRI scans were performed at baseline and at three, six, nine, 12 months and annually thereafter. We considered a lesion to be irreversible if it remained visually detectable on T2-weighted images for at least 1 year, if surrounded by normal or hyperintense grey matter and considered a lesion to be a PBH if the hypointensity was confirmed at the last available scan (where each potential hypointensity needed to be observed for a period of at least 1 year).

Statistical Analysis: Following season-adjustment, we modeled 25(OH)D using a time-dependent cumulative average, updating 25(OH)D using seasonally adjusted 25(OH)D measurements to assess the association between 25(OH)D and the number of new PBHs that developed after the 6 month MRI assessment. We considered 25(OH)D as a continuous (per 50 nmol/L) and categorized (≤50 nmol/L; >50 nmol/L) measurements. We modeled lesion counts using negative binomial models and logistic regression models to assess the proportion of lesions evolving into PBHs and accounted for intra-patient correlation using generalized estimating equations. Statistical Analysis: As described above.

Results: Overall, between categories of 25(OH)D included patients were roughly similar with respect to age, gender, EDSS (Table 1). Patients with higher 25(OH)D levels tended to have a lower BMI and higher central brain volume.

We observed generally similar associations between ≥50nmol/L and >50nmol/L levels and specific type of lesion at presentation (for Gd-enhancing lesions with nodular presentation: 0.94; 95% CI: 0.47-0.98; for Gd-enhancing lesions with ring presentation: 0.79; 95% CI: 0.47-1.35; for new T2 lesions with T2 hypointensity: 0.50; 95% CI: 0.30-0.81; for new PBH lesions isointense on T1: 0.83; 95% CI: 0.47-0.85).

Conclusion: Our results suggest vitamin D may also contribute to preventing neurodegenerative processes in MS.

Disclosures

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Vitamin D and the Development and Evolution of Permanent Black Holes Among Patients with Clinically Isolated Syndrome

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Abstract

We also assessed the association between 25(OH)D and number of lesions of mutually exclusive subtypes at initial presentation, locations and sizes and adjusted analyses for age, sex, treatment, baseline T2 lesions, and CIS onset type.