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Research Article

Vitamin D and Disability in Relapsing-Remitting Multiple Sclerosis

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Abstract

Background: Several studies have shown an inflammatory and immunomodulatory role of vitamin D in autoimmune diseases, which, includes an inhibition of the proliferation and expression of specific T lymphocytes, T cells regulation, and attenuation of the immune response. An inverse correlation between vitamin D levels and the degree of disability and relapse caused by Multiple Sclerosis (MS) has been documented in patients of mostly European background.

Objective: The objective of this study was to determine whether an association between vitamin D levels and clinical scores of disease in patients of Mexican background with Relapsing-Remitting MS (RRMS).

Methods: A cross-sectional study was conducted on 50 RRMS patients from the National Institute of Neurology and Neurosurgery in México City. All of the included RRMS patients were of Mexican background. The Expanded Disability Status Scale (EDSS) score, Progression Index (PI) and Annual Relapse Rate (ARR) were recorded for each patient during the initial visit. Vitamin D levels were assessed during the summer only. Pearson´s test was used to evaluate the relationship between vitamin D and EDSS, PI, ARR and duration of disease evolution. Significance was considered when $p < 0.05$.

Results: Most were female (n=29, 58%). The mean vitamin D level was 22.3± SD 6.4 ng/ml in MS patients. The mean EDSS score was 2± SD 0.5. The mean ARR was 1.3 ±0.5 and the mean PI was 1.08 ±SD 0.6. The mean of time disease duration was 32.4 ±14.9 months. No correlation was found between vitamin D levels and EDSS score, ARR, PI or duration of disease in the summer.

Conclusion: No correlations between vitamin D levels and disability or disease progression were found in Mexican patients with MS. This result could be due to a hereditary factor Mexican associated with racial background.

Keywords: Multiple sclerosis; Vitamin D; Disability; Mexican Mestizo; Expanded Disability Status Scale

Background

Multiple sclerosis (MS) is a chronic inflammatory disease that is characterized by demyelination of the Central Nervous System (CNS) [1,2]. The prevalence of MS in Mexico has increased from an original estimate of 1.6 patients per 100, 000 to 12 patients per 100,000 inhabitants [3]. The immune system is considered one of the major targets of the disease, although MS does appear to have a multifactorial etiology [4,5]. Genetically, the expression of the class II HLA-DRB*1501 allele increases the risk of contracting MS by 3-fold [6]. Several ambient factors have been proposed to influence the progression of MS, including living in regions over 45° in latitude, poor sun exposure, contact with viruses and low serum vitamin D levels, among others [5]. Furthermore, several studies have indicated that vitamin D (cholecalciferol or 25-hydroxivitamin D) can have an inflammatory and immunomodulatory role in patients with autoimmune disease [7]. *In vitro* experiments have shown the presence of Vitamin D Receptors (VDR) in lymphocytes, glia and microglia cells and have indicated that these cells types can metabolize vitamin D. Some effects of VDR activity have been demonstrated to inhibit the proliferation and expression of specific T lymphocytes [8,9] , promote T cell regulation, and attenuate the immune response [10]. Two different studies that were conducted on large patient cohorts demonstrated that a low serum level of 25-hydroxyvitamin D is an important risk factor for the development of MS [11,12]. In contrast, in a recent Mexican case control study, no differences in vitamin D serum levels between MS patients and control patients were found [13]. Therefore, we concluded that racial background is an influential factor in the progression of RRMS. Numerous studies have also indicated that an inverse correlation exists between vitamin D levels and the degree of disability in MS patients [14,15]. However, these studies have mostly been done in European background patients. Therefore, in this study, we aimed to determine whether there is a relationship between 25-hydroxivitamin D levels and MS related markers of disability in Mexican RRMS patients.

Methods

Design and study sample

This cross sectional was approved by the Committee of

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Table 1: Demographic and clinical characteristics.

	Total	Female	Male	p=
RRMS patients	50	29 (58%)	21 (42%)	0.00
Age in years (mean/SD)	33.1 (±8.2)	32.2 (±8.8)	34.3 (±8.0)	0.00
Vitamin D level (mean/SD)	22.3 (±5.9)	23.1 (±6.1)	21.2 (±5.6)	0.00
EDSS	2.2 (±0.7)	2.2 (±0.6)	2.1(±0.5)	0.78
IP	1.0 (±0.6)	1.1 (±0.6)	0.9 (±0.6)	0.14
ARR	1.3 (±0.5)	1.2 (±0.4)	1.3 (±0.5)	0.82
Evolution time in months	33.2(±14.8)	33.1 (±14.1)	33.3 (±16.1)	0.87

EDSS= Expanded Disability Status Scale; NA=Not Apply; PI=Progression Index; ARR=Annual Relapse Rate.

Investigation and Ethics of the National Institute of Neurology and Neurosurgery in México City; all participants were informed of the objectives, development and procedures of the research, and all participants signed an informed consent. A total of 50 Relapsing Remitting Multiple Sclerosis (RRMS) patients were recruited from the Clinic of Multiple Sclerosis of the INNN. Clinical data and serum samples were obtained from participants during the summer (July and August). All of the RRMS patients self-identified with Mexican descent and all were diagnosed according to the criteria of McDonald [16]. Disability was measured using the Expanded Disability Status Scale (EDSS); Disease progression was measured using the Progression Index (PI: EDSS/years of evolution of the disease, value 0.4-0.6), and clinical activity was measured by the Annual Relapse Rate (ARR: number of relapses/year, value 0.8). The sample size was calculated based on a power of 92% and an alpha of 0.05 by convenience sampling.

Procedure

At the initial visit, each RRMS patient underwent a complete clinical history, and a certified neurologist determined the EDSS, PI and ARR. Serum samples were taken from patients during the second visit next day.

Vitamin D measurement and location

Blood samples were processed to obtain 25-hydroxivitamin D levels in the Laboratory of Hormone and Serum Levels of INNN by ARCHITECT 25-OH Vitamin D Chimiluminescence of Micro particles [17]. All serum samples were discarded after processing. There is no definitive international consensus regarding normal blood levels of vitamin D; therefore, we considered a level of <19 ng/ml= to be poor, a level 20 to 29 ng/ml=to be insufficient, and a level of >30 ng/ml = to be sufficient [7]. All serum samples were obtained between July and August in Mexico City, which is located at 19°15´N latitude, has temperate sub-humid weather and displays a UV index that can range from 0 to 1218.

Outcomes

The first outcome of the study included the vitamin D levels of RRMS patients. The second outcome was the correlation between vitamin D levels and disability, progression and activity in MS patients, based on EDSS, PI, and ARR. The final outcome was the correlation between duration in mouths of MS disease and vitamin D concentration.

Statistical analysis

Normality was assessed by using Kolmogorov-Smirnov testing based on continuous variables showing no significance. We calculated the mean, median and standard deviation of all continuous variables. Categorical variables were expressed as proportions, and comparisons were performed with a chi-square test. For variables with normal distribution, a t-test was performed, and for abnormal distribution was used no parametric analysis. Pearson´s test was used for to identify correlations between EDSS, IP, ARR and duration of evolution and vitamin D. Testing was adjusted by age and by gender, and we used simple lineal regression if a correlation was found to be significant. We used SPSS software for Windows, version 22.0 (IBM SPSS Statistics, USA), for all statistical analyses. A p value of less than 0.05 was statistically significant.

Results

We evaluated a total of 50 patients, including 29 (58%) women and 21 men (42%). The clinical characteristics are shown in Table 1. The mean EDSS score was 2 ±0.5. The mean ARR was 1.3 ±0.5, and the PI was 1.08 ±0.6. The average duration of disease evolution was 32.4 ±14.9 moths.

Vitamin D

No significant differences were found in the study population in vitamin D levels or EDSS (p=0.200). The average vitamin D serum level was 22.3 (±5.9) ng/ml. Vitamin D levels that were considered sufficient (>30 ng/ml) were observed in 14% (n=7) of the patients. Levels that were considered insufficient (<29 ng/ml) were observed in 57% (n=27) of the patients, and levels considered poor < 19ng/ml were observed in 32% (n=16) of the patients.

There were no differences in vitamin D levels with respect to EDSS (p=0.80), PI (p=0.60) or ARR (p=0.13) by gender, but there was a difference in serum levels of vitamin D between females (23.1, ±6.1) and males (21.2, ±5.6) [CI 95% 20.8-25.5, p=0.000]. The results of these analyses are listed in (Table 1). No correlation was found between vitamin D levels and EDSS score, ARR, PI or duration of disease (Table 2). However, an analysis by gender indicated a moderate negative association between vitamin D levels and EDSS in females (r=-0.521, p =0.00), but with a low adjusted correlation (R2 = 0.272), Graphic 1 and 2.

Table 2: Correlation of vitamin D level with disability, progression and activity of RRMS.

	Total		Sub-groups			
	Correlation coefficient	p	Correlation Coefficient F	p	Correlation Coefficient M	p
EDSS	-0.159	0.27	-0.521	0.00*	0.329	0.62
PI	0.103	0.47	0.135	0.48	0.17	0.93
ARR	-0.1	0.46	-0.011	0.95	-0.209	0.35
Evolution time in months	-0.15	0.29	-0.268	0.16	0.003	0.99

*Significant Difference.

Discussion

All patients had low vitamin D serum levels and no correlation was found between hydroxyvitamin D and disability, relapse activity, progression or duration of the disease evolution. A small negative association was found between vitamin D levels and EDSS in female subjects, but it was not robust enough to be considered a disease predictor.

It is possible that low vitamin D levels in Hispanic MS patients result from environmental causes (diet, low consumption of fish, variable solar radiation, etc): however, racial background seems to be the primary factor responsible for the different levels that have been observed. Other studies that have been conducted on Hispanic MS patients have also indicated that these patients have low vitamin D levels, which were even lower than in Caucasians patients [19]. It should be noted that the Hispanics patients in the above referenced studies lived in North America, whereas the patients in our study lived in Latin America, which has different environmental characteristics, including latitude, UV radiation and diet which we would expect higher vitamin D levels [19-21]. Mowry had a subset of Hispanics in her dataset and their showed no association with levels of Vitamin D. Although pediatric, it still needs to be discussed.

We did not find a correlation between vitamin D levels and disability, relapse rate or disease progression. Our findings do not suggest a relationship. Those correlations specifically absent in this Hispanics population may be due to genetic factors, such as polymorphism variability in the gene that encodes the Vitamin D Receptor (VDR) also suggested by other authors [19]. There are 4 known types of VDR Single Nucleotide Polymorphisms (SNP), and the ApaI and FF FokI genotypes have been shown to present the most significant MS risk factors [22]. A lack of VDR expression could explain the inconsistent correlations between vitamin D levels and disability in Hispanic MS patients; however, further genetic testing in Hispanic MS patients must be performed before such conclusions can be made.

Of interest, we did find a correlation between vitamin D levels and disability in the female subjects. An explanation behind this finding may be that responses to vitamin D are hormone dependent. The immunomodulatory and anti-inflammatory effects of vitamin D were also apparent in female versus male MS patients [23].

The study has several limitations, including the convenience sample recruitment. Additional limitations include highly selective sample characteristics; Mexican background, low EDSS and younger age. Although these criteria strengthened the internal validity of our findings, their selectivity makes it difficult to generalize our results to all Hispanics. Therefore, in the future, it will be important to examine the relationship between vitamin D levels and disability longitudinally, and include ancestry and VDR polymorphism assessment in a larger sample of MS patients of Hispanic background.

Conclusion

In Mexican MS patients, no correlations between vitamin D levels and disability or disease progression were found. These findings may be attributable to an inherent hereditary factor that could be related to ethnic background.

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