Role of Vitamin D in the Pathogenesis of Multiple Sclerosis

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory demyelinating autoimmune disease of the central nervous system (CNS) with heterogeneous clinical presentations and course. While the exact aetiology of MS remains unknown, epidemiological data implicate that both genetic and environmental factors may be responsible for the aetiology of MS, with various factors interacting with one another. The environmental factors might start to occur, and also continue, long before the disease becomes clinically evident; hence we seek by our study to examine serum levels of vitamin D, proposed as an important environmental risk factor, in patients with multiple sclerosis and to find a relationship between vitamin D levels and the occurrence of MS. Vitamin D (25- hydroxy vitamin D/25(OH) D) was measured by ELISA in the serum samples from 29 patients with multiple sclerosis compared to non- multiple sclerosis subjects; low vitamin D levels was found in the MS patients especially female patients compared to 29 non- multiple sclerosis subjects.
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1. Introduction

The pathogenesis of multiple sclerosis still remains an uncertainty despite many years of investigation. Evidence for a single responsible cause is deficient: much doubt remains regarding the actual pathological impact of the many reported insults to the immune system (1).

Theories of the causes of MS have changed from the earlier understanding of a T cell-mediated demyelinating disease of the white matter of the nervous system to include a wide range of immunopathogenic mechanisms, axonal damage, and widespread grey matter pathologyand also on the controversial theory of chronic cerebrospinal venous insufficiency (2).

Neuronal death (axon loss) is present early in the disease course and is the predominant feature as the disease develops over time. It is hypothesized that loss of axons is the main mechanism underlying the progressive disability (3). New investigations reported that multiple sclerosis plaques are commonly located around central nervous system blood vessels leading to alternation of the blood-brain barrier permeability (1).

Recent epidemiological work has focused on the possible contributing environmental factors such as: vitamin D, sunlight and Epstein-Barr virus (4).

Besides its role as a calcium homeostasis modulator, vitamin D in addition has numerous potential extra-bone actions as: protective for the cardiovascular system, anti-proliferative (in certain cancers), anti-infectious (innate immunity), anti-inflammatory and immunomodulatory (adaptive immunity); an effect which could be involved in many autoimmune diseases such as type I diabetes, Crohn's disease, rheumatoid arthritis and MS (5).

Hence, this can be explained by the widespread of vitamin D receptors (VDRs) in almost all cells of the organism including immunity cells and all types of CNS cells and the expression of the1α-hydroxylase enzyme in these cells (5).

Those various emerging therapies are rapidly expanding the treatment options, including both parenterally administered and oral medications. Approaches to preserve tissue, promote healing and restore function are all under development and it is expected that this will provide better choices for patients especially with progressive disease (2).

Aim of the work:

We aimed to measure the concentrations of vitamin D in the sera of multiple sclerosis patients and non- multiple sclerosis subjects and to investigate the relationships between levels of vitamin D and the presence of MS.

Sample Collection:

All cases were recently diagnosed as multiple sclerosis patients, while the control group were non- multiple sclerosis subjects. Samples were stored at -20ºC till analysis.

2. Subjects and Methods:

Subjects

We involved 58 subjects in this study 29 multiple sclerosis patients (16 females and 13 males,

mean age 36.14 ± 2.1 years) were compared with non- multiple sclerosis subjects considered as control group (17 females and 12 males, mean age 37.18 ± 1.8 years). All multiple sclerosis patients were newly diagnosed.

Clinically, patients complained of limb weakness, dysarthria and spasticity.

Methods

Assay of serum 25-hydroxy vitamin D by enzyme-linked immunosorbent assay using a competitive protein binding assay kit for the measurement of 25-hydroxy vitamin D, which is based on the competition of 25-hydroxy vitamin D present in the sample with 25-hydroxy vitamin D tracer.

According to current recommendations, serum 25-hydroxy vitamin D levels less than 30 and less than 10ng/ml were defined as vitamin D insufficiency and vitamin D deficiency, respectively, while levels more than 30ng/ml weredefined as vitamin D sufficiency (6).

Data Handling and Statistical Methods

The statistical software package (SPSS version 10.0) was used for data management and analysis. Data were expressed as mean ± standard deviation. The data were subjected to the Kolmogorov- Smirmov test to determine the distribution and method of analysis.

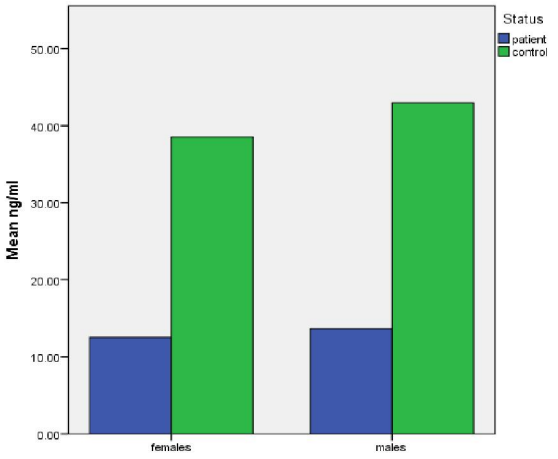
As most of the data was normally distributed continuous variables student's *t* test was used. To exam the correlation, Pearson's correlation coefficient's (r) were calculated by linear regression analysis. *p* values < 0.05, < 0.01 and < 0.001 were considered significant, highly significant and very highly significant respectively.

3. Results:

Table (1) demonstrates the total mean and ± SD of vitamin D in the sera of various studied groups; the total mean vitamin D levels were significantly lower (13.04± 0.93ng/ml) in the patient group compared to the total mean vitamin D levels in non-multiple sclerosis subjects (40.36 ± 5.76 ng/ml, $p<0.001$).

Table (2) shows the comparison of mean and ± SD of vitamin D in the sera of the females/ males of the studied groups; vitamin D levels of the female patients (12.53± 0.80ng/ml) compared to the female non-multiple sclerosis subjects (38.53 ± 4.15ng/ml, $p<0.001$) and in the male patients (13.66 ± 0.67ng/ml) compared to the male non-multiple sclerosis subjects (42.95 ± 6.85ng/ml, $p<0.001$).

Graph (1) demonstrates the comparison of mean and ± SD of vitamin D in the sera of the females/ males of the studied groups.



Graph (1) Mean of vitamin D sera levels (ng/ml) in female (patient /control groups) and in male (patient/control groups)

Table (1)Total mean and ± SD of vitamin D in the sera of the various studied groups.

Variable	Total mean (SD) vitamin D (ng/ml)		*t* statistics (df)	*p* value
	Patients	Control		
Vitamin D	13.04 (±0.93)	40.36 (±5.76)	-25.23 (29)	< 0.001

Table (2)Comparison of the mean and ± SD of vitamin D in the sera of the females/ males of the studied groups

	Control N= 29(ng/ml)	Patients N=29	*p* value
Female	38.53 (±4.15)	12.53 (±0.80)	< 0.001
Male	42.95 (±6.85)	13.66 (±0.67)	< 0.001
Total mean	40.36 (±5.76)	13.04 (±0.93)	< 0.001

4. Discussion:

The aetiology of Multiple sclerosis (MS) is still unknown and multifactorial.

Inflammation of the central nervous system is thought to be an essential component in the initiation of the disease. The specific elements that start this inflammation are still not fully known.

Both types of immune responses are thought to be involved in the pathogenesis of MS, the innate system plays a role in the initiation and progression of MS by influencing the effector function of T and B cells. The interaction between the antigen presenting cells (APCs) and the T cells is a chief component to initiate the adaptive immune response. Also, B cells polyclonal antibodies produced by the plasma cells are claimed to be found in the cerebrospinal fluid (CSF) of MS patients (7).

Studies have suggested that genetic, environmental and infectious agents might be also be among the factors influencing the development of MS (8) especially in the presence of patches of inflammatory plaques with demyelination of axon and oligodendrocyte loss and axonal injury (3). This myelinoclastic plaque-forming mechanism which is operative only in the central nervous system possibly also contributes to the pathogenesis of MS (1).

The axonal injury is increasingly recognized as the main pathological associate for the progressive neurological disability in MS. Recent studies have demonstrated axonal damage not only in the chronic demyelinated axons but also axonal damage and inflammation may occur in acute grey and white matter lesions sometimes may also diffuse to the normal-appearing white matter. Neurofilaments (NFs) are major structural proteins of the neurons. They are heavily concentrated in the axons. Several studies have now demonstrated the presence of NF peptides in the CSF of MS patients suggesting their release from the degenerative axons as a result of the MS disease process (3).

An alteration of the blood-brain barrier, resulting from various mechanisms including: trauma to the nervous system, immunological changes resulting from viral infections or vaccinations; all suggesting that the former observation of only immune system responsibility for the developing of MS must be re-evaluated. More evidence has been supporting the idea that the alteration of the blood-brain barrier permeability is a compulsory step in the development of the MS inflammatory plaques (1).

Among the risks, are the genetic factors which have been identified; in particular some susceptibility appears to exist in the histocompatibility complex of the human leucocyte antigen (HLA) (9). Susceptibility studies of families and twins have shown a 40 fold increased susceptibility among first degree relatives of MS patients, confirming a genetic factor (8).

Infectious environmental risk factors, mainly past infections with Epstein-Barr or related virus, vitamin D deficiency and cigarette smoking may also present the commonest potential non-genetic risk factors. The effects of latitude, climate and diet have successively been considered. Exposure to all these multiple risk factors can lead to the clinical appearance of the disease (10).

Epstein-Barr virus (EBV) is believed to be the strongest known pathological risk factor for MS compared with uninfected individuals; the hazard of developing MS is approximately 15 fold higher among individuals infected with EBV in childhood and about 30 fold higher among those infected with EBV in adolescence or later in life (11).This can be explained by the molecular similarity of the pathogens peptides with direct sequence homologies with the myelin components of the axon (12).

Both experimental and clinical observations provide evidence that vitamin D is also one of several important environmental factors that can affect multiple sclerosis manifestation. A protective effect has been supported by reduced risk of the illness associated with sunlight exposure (9).

Our study was done to assess levels of 25-hydroxy vitamin D in the sera of multiple sclerosis patients. Our results showed that the total mean of sera 25- hydroxy vitamin D is significantly lower (13.04± 0.93ng/ml) in the patient group compared to the total mean 25- hydroxy vitamin D levels in non-multiple sclerosis subjects (40.36 ± 5.76 ng/ml, $p<$ 0.001), in agreement with previous work (9).

On the other hand, Dseilligny and Souberbielle have emphasized that the specific role of vitamin D within CNS cells remains to be clarified: it may have potential actions in neuronal functioning, neuroprotection and myelination, and also in innate and adaptive immunity of the CNS, through the invading lymphocytes (5).

Multiple sclerosis is a chronic disabling disease of the central nervous system commonly affecting young adults especially females. Our current results coincide with the previous observations that multiple sclerotic female patients (12.53± 0.80 ng/ml) had lower levels of hydroxy vitamin D than multiple sclerotic male patients (13.66 ± 0.67ng/ml). An observation confirmed by other researchers by doing magnetic resonance imaging characteristics of the lesions occurring in the brain of 413 MS patients: men patients had fewer contrast-enhancing lesions (p = 0.01), but a higher proportion of lesions evolving into ‘black holes’ (p =

0.001), when compared with women patients. The data indicated that men with MS are prone to develop less inflammatory, but more destructive lesions than women (13).

Higher vitamin D status in men than women can likely be explained by different cultural behaviour; as outdoor activity, protection from sunlight exposure and dietary habits that may also contribute to these differences. This study and our results support the suggestion for the MS pathological changes related to gender(14).

Populations located at high latitudes and consumed high vitamin D rich food were observed to have reduced MS prevalence, while the risk of MS incidence decreased with movement from high to low altitudes (15).

Epidemiological data also support a potential relationship between vitamin D deficiency and an increased risk of developing MS. Previously in vitro studies have expanded the potential role of vitamin D and its receptor beyond its classical calcium modulation, regulation, and maintenance of bone mineralization, to include immune modulation (16).

The prevalence of vitamin D essentiality can be explained by the extensive spread of the VDRs in almost all cells including immunity cells and all types of CNS cells. These different immune and nervous cells express the 1α-hydroxylase enzyme which is able to transform in situ the circulating 25-hydroxyvitamin D (25-OH-D) into calcitriol (1 α,25-$(OH)_2D_3$)- the active metabolite of vitamin D, resulting in intracrine and paracrine actions in these cells and other neighbouring cells (5).

Accordingly, the importance of VDRs and 1α-hydroxylase enzyme in the different immune and nervous cells constitutes a first indication for potential deprivation of vitamin D in MS. Hence, the immunodulatory action of vitamin D through the general immune system is likely to be important for the MS pathogenesis (5).

Activated macrophages produce 1α, 25-dihydroxyvitamin D_3 (1 α, 25-(OH) $_2D_3$), and the expression of VDRs by the immune system cells, suggests the influence of vitamin D endocrine system on the immune system functions (17).T cells themselves are described to have VDRs; direct T cell inhibition is another hypothesized molecular mechanism of vitamin D effect on MS pathology (18).

Earlier studies done in animal models of multiple sclerosis (MS), insulin-dependent diabetes mellitus (IDDM), inflammatory bowel disease (IBD) and transplantation, proved that 1 α, 25-$(OH)_2D_3$ increase the function of regulatory- suppressor T cells populations with the capacity to inhibit inappropriate immune responses that cause disease; confirming that absence of 1 α, 25-$(OH)_2D_3$ may encourage the appearance of diseases including MS (17, 19).

Conclusion

Further research is needed to establish mechanisms of the exact causality of MS in humans and hence discover preventative strategies.The therapeutic effects of vitamin D supplements to MS patients need further to be investigated.

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