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Commentary

Multiple Sclerosis Pathogenesis: Possible Interplay between Vitamin D Status and Epstein Barr Virus Infection

Giulia Bivona[1,2], Concetta Scazzone[1,2], Bruna Lo Sasso[1,2], Rosaria Vincenza Giglio[1,2], Caterina Maria Gambino[1,2], Luisa Agnello[1], Marcello Ciaccio[1,2,*]

[1]Department of Biomedicine, Neurosciences and Advanced Diagnostics, Institute of Clinical Biochemistry, Clinical Molecular Medicine and Clinical Laboratory Medicine, University of Palermo, 90127 Palermo, Italy
[2]Department of Laboratory Medicine, University Hospital "P. Giaccone", 90127 Palermo, Italy
*Correspondence: marcello.ciaccio@unipa.it (Marcello Ciaccio)
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The role of vitamin D, Epstein Barr Virus (EBV), and endogenous retrovirus (ERV) in the pathogenesis of multiple sclerosis (MS) has been addressed in recent literature. Some authors hypothesized that a synergistic interplay between these factors could favor the onset and progression of the disease [1]. However, it seems that some considerations to better define this relevant topic should be expressed.

1. Vitamin D

Vitamin D is a nutrient that can be taken by diet and an endogenous steroid hormone regulating hundreds of gene expressions [2]. Beyond the regulation of calcium and phosphate metabolism and immune response, the active form of vitamin D can modulate brain function during development and in adulthood [3,4]. Hence, vitamin D deficiency has been broadly investigated in autoimmune, neurological, and neuropsychiatric diseases, both as a risk factor for developing some disorders or as a biomarker to identify specific features, including severity.

Before specifying the biological activities of vitamin D, it is worth mentioning the steps of its metabolism, since many roles of the hormone have been revealed after the discovery that many tissues and cells are capable of synthesizing and receiving vitamin D. Ultraviolet B rays (295–310 nM) transform the cutaneous precursor 7-dehydrocholesterol into cholecalciferol, which requires two sequential hydroxylations to form the active vitamin D3. The first hydroxylation produces 25-hydroxyvitamin D (25(OH)D) in the liver through the action of 25-hydroxylase. The 1-α-hydroxylase enzyme carries out the second hydroxylation, forming vitamin D3 (1,25(OH2)D) in the kidney, prostate, placenta, lung, brain, and immune cells. The enzymes involved in vitamin D metabolism mostly belong to the cytochrome P450 (CYP450) family. CYP2R1, CYP3A4, and CYP27A1 enzymes have 25-hydroxylase activities, whereas CYP27B1 is responsible for 1,25 hydroxylation [5]. Although the renal hormone drives calcium metabolism in an endocrine fashion, the extra-renal one acts in an autocrine/paracrine fashion and is responsible for the regulation of immune response and brain function.

The nuclear receptor of active vitamin D (VDR) binds to the membrane-associated rapid-response steroid-binding proteins (MARRS) or protein-disulfide-isomers family A members 3 (PDIA3), although a surface receptor is known as well [6]. After the binding of active vitamin D, VDR and MARRS carry on, respectively, the genomic and non-genomic actions of vitamin D [7].

As Brutting *et al*., found [8], low blood 25(OH)D levels have been widely reported in the healthy population, but vitamin D reference values are still a controversial topic. Vitamin D sufficiency is defined as a serum 25(OH)D level equal to or higher than 30 ng/mL, whereas vitamin D insufficiency is described as a serum 25(OH)D level from 20 to 30 ng/mL, and deficiency is described as lower than 20 ng/mL. Note that the optimum level to maintain skeletal health is defined as sufficiency, although no optimum for vitamin D status has been identified when considering the immunomodulation activities of the hormone [9]. In other terms, the vitamin D blood levels that are required to maintain proper immune or brain function are still debated. Indeed, as for some other analytes, no consensus on serum 25(OH)D reference intervals exists due to the lack of a standardization process [10].

Active vitamin D influences the immune system in different ways, but generally it can be said that the hormone drives the balance between anti-inflammatory and pro-inflammatory immune responses. Briefly, the immunomodulating activities of vitamin D can be described as follows: vitamin D can modulate the expression of CD14 and TLR4 co-receptor in macrophages and keratinocytes. VDR and 1,25(OH)2D are expressed by macrophages, dendritic cells, and activated B and T lymphocytes. The role of active vitamin D in the differentiation of dendritic cells is open to discussion, although it is known that it can lower their antigen-presenting capacity and survival [7,11].

The 1,25(OH)2D plays a key role in T-helper (Th) Th1, Th2 and Th17 lymphocyte balance by inhibiting the production of Th1 and Th17 cells and their cytokines, and enhancing the differentiation of Th2. Further, 1,25(OH)2D fosters the development of T- regulatory (T-reg) cells and the production of their cytokines [12].

Due to the immunomodulatory activity of vitamin D, it acts against pathogens in many ways: (a) it induces the expression of cathelicidin and defensins, which are antimicrobial peptides involved in the defense against microorganisms [6,12]; (b) it increases the antimicrobial activity of the innate response; and (c) it decreases adaptive pro-inflammatory effects.

However, the main impact of 1,25(OH)2D on the defense against pathogens is modulating Th lymphocyte subset balance, which is particularly important since Th balance and T-reg cells function both affect the efficacy and safety of immune responses against pathogens.

2. Vitamin D and MS

MS is a chronic autoimmune disease of the central nervous system and represents the most common cause of non-traumatic disabling in young adults [13]. Demyelination and axonal degeneration are characteristics of the disease. As for other neurological diseases, robust data from large genome-wide association studies support the role of genetics as one of the most significant risk factors for MS [14,15]. However, the impact of environmental factors on the etiology and pathogenesis of the disease is well-established, and many efforts have been made in past decades to identify possible environmental risk factors for MS. One of the most studied environmental risk factors for MS is vitamin-D-poor status.

It is interesting that among gene variants associated with MS risk, some are involved in the metabolic pathway influencing vitamin D status. An extensive dissertation on all vitamin D-related gene variants that have been evaluated in MS patients goes beyond of the scope of this commentary. However, the single-nucleotide polymorphisms of VDR have been largely investigated with some positive association to the risk of disease development, whereas research on others, including CYP27A1, CYP3A4, CYP27B1, CYP24A1, produced more controversial finding [16,17].

Beyond genetic investigations, several studies have addressed the question of whether low vitamin D levels could be a risk factor for the onset of the diseases or a biomarker for disease severity in MS patients [17].

Vitamin D levels have been reported in patients affected by MS in both neonatal and adult cohorts [18–20]. A large multi-center, randomized trial showed that serum 25(OH)D level is a strong risk factor for long-term MS activity and progression in the early disease course, and seems to predict new active lesions and relapse rate [21]. Munger *et al.* [18] found that low 25(OH)D levels ($<$30 nmol/L) were associated with a higher MS risk than were normal levels ($\geq$50 nmol/L). Although these findings could seem encouraging, it should be noted that 25(OH)D measurement was performed by chemiluminescence assay, whereas liquid chromatography-tandem mass spectrometry methods should be used to measure 25(OH)D, according to the National Institute for Standard and Technology recommendations [22]. The standardization issue for 25(OH)D measurement is the main reason there is no evidence-based consensus by which 25(OH)D values define vitamin D insufficiency, deficiency, and sufficiency. The lack of standardized data has hampered reaching univocal findings on the role of vitamin D in disease, and MS is not an exception.

3. Vitamin D, a Putative Link Bridging EBV, ERV and MS

Vitamin D levels have been studied in patients affected by respiratory tract infections, tuberculosis, virus infections (Human Immunodeficiency Virus, EBV), parasitic, and fungal infections in both adults and children, both as a risk factor and as a supplementation adjuvant therapy [11].

The relationship between vitamin D and EBV infection has been evaluated mainly in patients affected by MS, because EBV infection is one of the most studied environmental factors involved in the pathogenesis of the disease [23]. Several direct and indirect mechanisms have been hypothesized to explain the susceptibility of patients with mononucleosis, which is caused by EBV, to MS onset. Many studies reported high levels and frequencies of EBV antibodies in MS, but the presence of EBV is almost ubiquitous in adults, which weakens the hypothesis [24]. Further, assay methods used to detect antibodies in MS patients can influence the strength of the results to some extent. It is important to note that the presence of low vitamin D in healthy people, together with the lack of standardized data from affected ones, represent two main pitfalls weakening the findings available on this topic. Also, it should be remembered that, during chronic inflammatory disease, as MS is, many analytes can change without an established causal link between the disease and the molecule variation, due to the reverse causation issue [25,26].

Finally, ERV expression has also been related to the risk of MS onset; MS patients have been found to overexpress RNA from the HERV-W ERV family relative to healthy controls [14]. Molecular mechanisms underlying the relationship between ERV expression and MS onset include, among others, the expression of proteins from ERVs that induce pro-inflammatory cytokines (such as TNFα) [27]. Also, EBV infection has been reported to trigger the expression of HERV-W loci [27]. However, it seems that no conclusions can be drawn on this issue. Indeed, from a strictly theoretical point of view, the interplay among low vitamin D status, MS, EBV, and ERV, could be referred to as a pro-inflammatory *milieu* that could facilitate the etiopathogenesis mechanisms involved in the onset of

the disease. However, this scenario makes more likely the hypothesis that vitamin D, EBV, and ERV are pieces of a larger and composite mosaic that seems yet to be understood.

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GB—extraction and drafting of the manuscript; CS, BLS—analysis of data; LA, CMG, RVG—manuscript revision; GB, MC—design and revision.

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Conflict of Interest

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