EXPERT REVIEWS

Vitamin A: yet another player in multiple sclerosis pathogenesis?

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Massimo Filippi*, Paolo Preziosa and Maria A Rocca

Neuroimaging Research Unit and Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, via Olgettina, 60, 20132 Milan, Italy
**Author for correspondence:*
Tel.: +39 02 264 33054
Fax: +39 02 264 33031
filippi.massimo@hsr.it

Evaluation of: Løken-Amsrud KI, Myhr KM, Bakke SJ *et al*. Retinol levels are associated with magnetic resonance imaging outcomes in multiple sclerosis. *Mult. Scler.* doi:10.1177/1352458512457843 (2012) (Epub ahead of print).

A combination of genetic and environmental factors probably plays a role in determining an increased susceptibility to multiple sclerosis (MS). Among these factors, vitamin D and A metabolites are likely to play a role given their immunomodulatory properties. Decreased serum vitamin D levels have been associated with clinical and MRI activity of MS. Løken-Amsrud *et al*. evaluated the association of retinol concentration with clinical and MRI measures of disease activity in MS patients over a 2-year period. Serum retinol levels correlated with MRI metrics of disease activity, but not with clinical findings. Following IFN-β-1a treatment, the association with MRI metrics was lost. These results support a role of vitamin A metabolites in influencing disease activity in MS.

Keywords: interferon • MRI • multiple sclerosis • relapse • retinol

Multiple sclerosis (MS) is a demyelinating and neurodegenerative disease of the CNS, which is one of the main causes of irreversible neurologic disability in young adults [1]. MS is notoriously heterogeneous in terms of clinical manifestations and evolution, as well as in terms of its immunopathological substrates.

The last few decades have witnessed a major effort to identify the factors associated with MS onset and progression. Although there is mounting evidence that a combination of genetic and environmental factors plays a role in determining an increased susceptibility to MS and its clinical evolution, the etiology and pathophysiology of this condition are still largely unknown. Among the different and potentially relevant environmental factors investigated so far, it has been suggested that lipophilic hormones, such as vitamin D and vitamin A metabolites, may have immunomodulatory properties, and therefore influence the course and severity of MS [2].

Vitamin D status may contribute to explain the well-known impact of geographic location on MS incidence, which is low in equatorial countries and high in areas of the world with reduced sunlight exposure [3]. Decreased serum vitamin D levels have been associated with an increased risk of relapses in patients at presentation with a clinically isolated syndrome suggestive of MS and in patients with relapsing–remitting MS [4]. Recently, it has been found that higher vitamin D levels correlate with a lower risk of developing new T2 and gadolinium (Gd)-enhancing lesions on MRI scans over a 5-year period [5].

Vitamin A, which is obtained from the diet as retinol, retinyl esters or β-carotene, is known to exert pleiotropic effects by binding to the nuclear retinoic acid receptor family, retinoid X receptors and peroxisome-proliferator-activated receptor. As a consequence, vitamin A is likely to modulate a broad range of immune processes, which include the following: antigen presentation by exerting a direct effect on dendritic cell function; proliferation, differentiation, activation and apoptosis of T and B cells and functioning of microglia and astrocytes. Based on this, retinoic acid has been successfully used to treat various immune-mediated conditions, such as psoriasis and contact dermatitis. However, the role of vitamin A in influencing the risk of relapses in patients with MS has received little attention so far. Likewise, whether the supplementation of vitamin A may improve the clinical outcome of MS patients is still unknown.

Two studies have shown a reduction of retinol levels in patients with MS [6,7]. In the study by

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Besler *et al.*, MS patients were found to have lower β-carotene and retinol levels than healthy controls during the course of a relapse [6]. β-carotene levels were also inversely correlated with oxidative stress burden (as reflected by the detection of lipid peroxidation products). Royal *et al.* demonstrated that patients with MS have lower plasma retinol levels compared with patients affected by other neurological conditions [7]. Intriguingly, such abnormalities were less pronounced in MS patients treated with IFN-β-1a, suggesting that retinoic acid derivatives and IFNs may have a synergistic effect in modulating disease activity.

At present, only one study has assessed the association of retinol concentration with clinical and MRI measures of disease activity in patients with MS [8].

Methods & results

This is a 2-year follow-up study, which enrolled 88 relapsing–remitting MS patients from a randomized placebo-controlled trial of ω-3 fatty acids as an add-on treatment to IFN-β-1a (OFAMS study) [9]. Clinical evaluation (with disability assessed using the Expanded Disability Status Scale score) was performed every 6 months, and MRI scans were acquired monthly during the first 9 months of the study and then at months 12 and 24. Serial serum collection to quantify retinol levels was performed at baseline and at months 1, 3, 6, 7, 9, 12, 18 and 24. All patients started IFN-β-1a 6 months after study inclusion. Such a design allowed the group to assess the relation of retinol levels with clinical and MRI activity (new/enlarged T2 lesions and Gd-enhancing lesions) as well as the impact of IFN-β-1a treatment on these metrics.

The main results of this study can be summarized as follows:

- Retinol levels differed significantly between genders, with higher values found in men, but they were not correlated with age and IFN-β-1a treatment. No seasonal fluctuations were detected;
- Serum retinol levels were not associated to the number of relapses and to Expanded Disability Status Scale worsening;
- An increase of 1 μmol/l of serum retinol reduced the risk of developing new Gd-enhancing lesions by 49%, new T2 lesions by 42% and active lesions (a combination of the former two) by 46%;
- MRI outcomes were associated with retinol levels prior to initiation of IFN-β-1a treatment, but not after;
- All these findings were not influenced by vitamin D and ω-3 fatty acid levels or by *HLA-DRB51*15* genotype, which has been shown to interact with environmental risk factors for MS [10].

Expert commentary & five-year view

It is well known that MRI is the most objective and sensitive paraclinical tool for the diagnostic work-up of patients suspected of having MS and for the monitoring of disease evolution and treatment efficacy in patients with definite MS [11,12]. T2-weighted and post-Gd T1-weighted MRI scans provide quantitative pieces of information on subclinical disease activity, which occurs at a rate at least ten-times higher than that detected clinically. This might contribute to explain why MRI and not clinical metrics were correlated with retinol levels. Since several quantitative MRI-based techniques, including magnetization transfer and diffusion tensor MRI, are known to have a higher specificity to the heterogeneous pathological substrates of MS than conventional MRI [13], their use to quantify tissue damage in different brain compartments (lesions, normal-appearing white matter and gray matter) and at different stages of the disease might result in a better understanding of the role of retinoic acid in promoting remyelination and tissue repair.

A partially unexpected finding of the study by Løken-Amsrud *et al.* is the observation that, following treatment with IFN-β-1a, the significant association between retinol levels and MRI measures of disease activity was lost [8]. Such a finding, which might be due to a differential effect of IFN-β-1a treatment on these metrics, challenges the notion of a combined immunomodulatory effect of IFN and retinoids in patients with MS [14,15]. Clearly, this finding needs to be interpreted with caution, considering the significant reduction of MRI activity observed in this cohort of patients following treatment initiation. The use of novel MRI measures of MS burden, tailored to quantify not only the inflammatory components of the disease, but also its neurodegenerative features (e.g., quantification of atrophy), might reveal previously unrecognized aspects related to vitamin deficits in MS patients.

In conclusion, the demonstration of a possible role of vitamin A metabolites in influencing the risk of MS patients to experience phases of activity may contribute to the identification of those factors involved in the susceptibility to the disease, which in turn may have relevant clinical and therapeutic implications.

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Key issues

- Multiple sclerosis (MS) is a demyelinating and neurodegenerative disease of the CNS. Its etiology and pathophysiology are not yet completely understood.
- Several environmental factors have been suggested as potential susceptibility factors for MS.
- MRI is a sensitive paraclinical tool for the diagnostic work-up of patients suspected of having MS and for monitoring disease evolution.
- Vitamin A metabolites may play a role in determining the risk to develop clinical and MRI activity in MS patients.
- Conventional and advanced MRI techniques sensitive to the different pathological substrates of MS might improve our understanding of the physiopathology of this condition and contribute to shed light on the role of genetic and environmental factors involved in the clinical onset and progression of the disease.

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