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<https://doi.org/10.1016/j.nrleng.2020.05.018>  
2173-5808/

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## 25(OH)D3 deficit and multiple sclerosis: A simple epidemiological association or a true causal relationship<sup>☆</sup>



### Déficit de 25-OH-D<sub>3</sub> y esclerosis múltiple: una simple asociación epidemiológica o una verdadera relación de causalidad

Dear Editor:

Vitamin D deficiency is a true epidemic. Epidemiological studies indicate that the condition is more frequent above the 40th parallel north.<sup>1</sup> In humans, vitamin D is mainly synthesised in the dermis through the action of ultraviolet B radiation, which catalyses the photoconversion of 7-dehydrocholesterol to cholecalciferol; after hepatic hydroxylation, cholecalciferol is converted to 25-hydroxyvitamin D<sub>3</sub> (25-OH-D<sub>3</sub>) or calcifediol, which is the most abundant form of vitamin D<sub>3</sub> in the human body but is not biologically active. Subsequently, 25-OH-D<sub>3</sub> undergoes hydroxylation by 1- $\alpha$ -hydroxylase in the kidneys, forming the active metabolite 1,25-dihydroxyvitamin D<sub>3</sub>, also known as 1,25(OH)<sub>2</sub>D<sub>3</sub> or calcitriol. This metabolite acts by binding to vitamin D receptors. Vitamin D receptors located

in cell nuclei trigger so-called genomic actions, leading to protein synthesis, and non-genomic (rapid) actions, such as the induction of second messengers and the opening of ion channels.<sup>2,3</sup>

Various epidemiological studies have identified an association between low levels of 25-OH-D<sub>3</sub> and multiple sclerosis (MS).<sup>3,4</sup> It has also been reported that 25-OH-D<sub>3</sub> deficiency is associated with radiological disease activity, defined as the presence of new lesions on T2-weighted MRI sequences or contrast-enhancing lesions.<sup>5</sup> Finally, other studies indicate that vitamin D supplementation has a beneficial effect on these radiological parameters.<sup>6</sup> The biological plausibility of this association may be explained by a tolerogenic environment promoted by the anti-inflammatory and immunomodulatory effects of vitamin D.<sup>3,7</sup>

A recent epidemiological study on the prevalence of MS in the Spanish city of Ourense (latitude, 42° 34' N) recorded the highest rate reported to date in the Iberian Peninsula: 184 cases/100 000 population, approaching the figures recorded in more northerly countries with Anglo-Saxon influences. One mechanism favouring MS may be the presence of vitamin D deficiency, which is recorded in over 95% of patients with MS.<sup>8</sup> In the general population, 25-OH-D<sub>3</sub> deficiency is defined as levels < 14 ng/mL, with levels between 15 and 29 ng/mL considered to indicate insufficiency. Our laboratory's reference values for the active metabolite calcitriol are between 20 and 55 pg/mL.

We decided to analyse 1,25(OH)<sub>2</sub>D<sub>3</sub> in our population of patients with MS, determining levels in a randomised sample of 44 individuals. Median plasma levels were 15 ng/mL (range, 8–36) for calcifediol and 46.5 pg/mL (22–83) for cal-

<sup>☆</sup> Please cite this article as: García Estévez DA. Déficit de 25-OH-D<sub>3</sub> y esclerosis múltiple: una simple asociación epidemiológica o una verdadera relación de causalidad. *Neurología*. 2021;36:245–246.

citriol. 25-OH-D<sub>3</sub> levels were equal to or below 20 ng/mL in 32 patients (72.7%), and were only above the optimal value of 30 ng/mL in one patient (2.3%). However, 1,25(OH)<sub>2</sub>D<sub>3</sub> levels were above the lower limit of normality in all patients, with 17 (38.6%) presenting levels above the upper limit. Based on these data and the well-understood physiology of vitamin D, we may conclude that 1,25(OH)<sub>2</sub>D<sub>3</sub> levels are increased due to secondary hyperparathyroidism caused by decreased deposits of 25-OH-D<sub>3</sub>; as a consequence, this deficit may have no physiological or clinical impact, as the final pathway through which calcitriol acts is unaffected.

One issue arising from this analysis is the question of whether epidemiological studies exclusively evaluating the body's vitamin D deposits truly support the notion of vitamin D deficiency as a predisposing factor for MS. Specifically, all in vitro studies into the relationship between vitamin D and immune system regulation involve the action of 1,25(OH)<sub>2</sub>D<sub>3</sub>,<sup>7</sup> and studies into 25-OH-D<sub>3</sub> supplementation have been unable to reliably demonstrate changes in this regulation<sup>9</sup> or a reduction in relapse rates.<sup>6,10</sup>

In conclusion, given the current understanding of the physiology of vitamin D, we recommend vitamin D supplementation to achieve 25-OH-D<sub>3</sub> levels greater than 30 ng/mL in order to minimise the deleterious effects of secondary hyperparathyroidism on bone metabolism (osteomalacia). However, well-designed clinical trials are needed to justify long-term treatment with megadoses of vitamin D aiming to modify the clinical course of MS.

## Funding

This study has received no funding of any kind.

## Conflicts of interest

The author has no conflicts of interest to declare.

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<https://doi.org/10.1016/j.nrleng.2020.04.019>  
2173-5808/

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## Half and half syndrome as a presentation of multiple sclerosis ☆



## Síndrome del medio y medio como presentación de esclerosis múltiple

Dear Editor:

Half and half syndrome is a rare oculomotor disorder characterised by unilateral internuclear ophthalmoplegia (INO) and ipsilateral sixth nerve palsy. Its name refers to the impair-

ment of half of the contralateral gaze (secondary to INO, which limits adduction of the ipsilateral eye) and half of the ipsilateral gaze (secondary to a fascicular lesion to the abducens nerve, with no damage to the abducens nucleus, allowing normal contralateral eye adduction).<sup>1</sup> This is an extremely rare INO plus syndrome, which may hinder differential diagnosis of other acute or subacute oculomotor disorders.

We present the case of a 47-year-old man with no relevant medical history who visited our hospital due to a 6-day history of progressive sensory impairment, right faciobrachial hemiparesis, and horizontal diplopia. The neurological examination revealed horizontal diplopia when looking to the left, with the false image being generated by the left eye; this finding is compatible with left sixth cranial nerve palsy. We also observed limited adduction of the left eye when looking to the right (with preserved conver-

☆ Please cite this article as: Gómez Iglesias P, Sanesteban Beceiro E, Gómez Ruíz MN, Matías Guiu JA. Síndrome del medio y medio como presentación de esclerosis múltiple. *Neurología.* 2021;36:246–248.