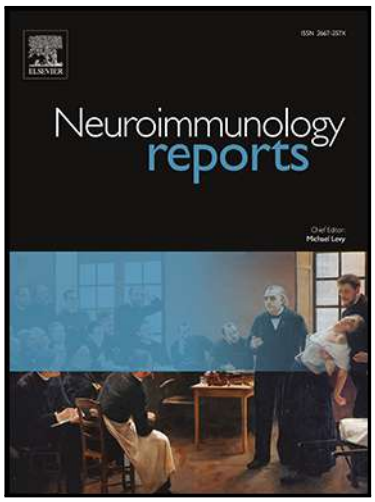
Journal Pre-proof



Resolution of Optic Neuritis and Probable Multiple Sclerosis after Long-Term Ingestion of Very High Doses of Vitamin D_3: A Case Report

Nipith Charoenngam , Michael F. Holick

PII: S2667-257X(24)00025-1
DOI: https://doi.org/10.1016/j.nerep.2024.100224
Reference: NEREP 100224

To appear in: *Neuroimmunology Reports*

Received date: 26 May 2024
Revised date: 10 July 2024
Accepted date: 27 July 2024

Please cite this article as: Nipith Charoenngam , Michael F. Holick , Resolution of Optic Neuritis and Probable Multiple Sclerosis after Long-Term Ingestion of Very High Doses of Vitamin D_3: A Case Report, *Neuroimmunology Reports* (2024), doi: https://doi.org/10.1016/j.nerep.2024.100224

Resolution of Optic Neuritis and Probable Multiple Sclerosis after Long-Term Ingestion of Very High Doses of Vitamin D_3: A Case Report

Article type: Case report

Authors: Nipith Charoenngam, MD[1, 2], Michael F. Holick, PhD, MD[1]

Affiliation

[1]Vitamin D, Skin, and Bone Research Laboratory, Section Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine, Boston University School of Medicine

[2]Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

*Corresponding author: Michael F. Holick, PhD, MD

Address: Vitamin D, Skin, and Bone Research Laboratory

Boston University School of Medicine

85 E Newton St, M-1013

Boston, MA 01228

E-mail: mfholick@bu.edu

Conflict of Interest

Michael F. Holick receives grants from Carbogen-Amcis and Solius Inc is a consultant for Solius Inc. and Biogena and is a member of the speaker's bureau for Pulse LTD, Sanofi, and Menarini Inc. Nipith Charoenngam has no conflicts of interest.

Funding

None

Short summary

A 36-year-old male presented with 2 months of left-eye visual disturbance and was diagnosed with optic neuritis due to probable multiple sclerosis (MS). He was advised to undergo periodic ophthalmology follow-up without immunosuppressive treatment. Due to persistent symptoms, he expressed interest in very high-dose vitamin D_3 therapy of 54,000 IUs/day (1,000 IUs/kg/day) along with a zero-calcium diet. After starting the therapy, he experienced sustained symptomatic improvement of visual symptoms over 4 years, along with radiological stability of the optic neuritis lesion without developing hypercalcemia. This case supports the potential therapeutic efficacy of very high-dose vitamin D for MS.

Introduction

Low concentrations of serum 25-hydroxyvitamin D [25(OH)D] is associated with an increased risk of multiple sclerosis (MS) (1-4). Consequently, vitamin D supplementation has been proposed as an adjunctive treatment for this condition. However, evidence from existing clinical trials is conflicting (5).

Administration of very high doses of vitamin D starting at 1,000 IUs/kg/day has been proposed by the Coimbra group in Brazil to have therapeutic efficacy for treatment of MS (6). However, data on its efficacy are scarce due to the absence of controlled clinical trials and concerns regarding its safety. In this report, we describe a patient with left-eye visual disturbance due to optic neuritis and probable MS. The symptoms resolved after he ingested 54,000 IUs/day of vitamin D_3 for several years.

Case description

A 36-year-old male with a past medical history of childhood viral meningitis presented with two months of progressive blurry vision in his left eye. Over the past two months, he has experienced a progressive loss of visual acuity and color desaturation in his left eye. On review of symptoms, he denied any prior episodes of vision changes, diplopia, focal weakness, or changes in speech or swallowing function, nor in bowel or bladder function. He took vitamin D_3 8,000 IUs/day and did not take any other medications. Upon examination, visual acuity was recorded as 20/20 in the right eye and 20/25-20/30 with pinhole correction in the left eye. Funduscopic examination revealed normal retina and optic disc in the right eye. However, the left eye exhibited visible gliosis at the disc margins and increased cupping without pallor. Pupils were equal and reactive to light. No ptosis or nystagmus was observed, and extraocular movements were intact. The remainder of the neurological examination was unremarkable.

A brain and orbit MRI revealed T2 signal abnormalities in the left optic nerve and multiple T2 hyperintense white matter lesions (**Figure 1A**). Additionally, an MRI of the cervical and thoracic spine demonstrated a nonenhancing T2 hyperintense lesion in the cervical cord at the C4-5 level. Further workup was negative for HIV, HBV, HCV, anti-SSA/SSB, ACE, anti-NMO, anti-MOG, interferon-gamma release assay and Lyme antibody. Hemoglobin A1C, thyroid-stimulating hormone and vitamin B12 levels were normal. Serum 25(OH)D concentration was previously 13 ng/mL, which increased to 31 ng/mL with vitamin D supplementation.

He subsequently underwent a lumbar puncture. His cerebrospinal fluid (CSF) profile was significant for elevated CSF/serum IgG index at 1.31 (normal range ≤0.85) upon oligoclonal band testing. He was then diagnosed with optic neuropathy secondary to retrobulbar optic neuritis and probable MS. However, he did not meet the definitive diagnostic criteria for MS due to the absence of dissemination in time. Considering the time course of his presentation and the

lack of other acute neurological symptoms, steroid therapy was not recommended. He was advised to undergo periodic ophthalmology follow-up.

Due to the lack of improvement in his symptoms, he sought alternative therapy and expressed interest in using high-dose vitamin D. Understanding the potential side effects associated with vitamin D toxicity, he presented to the endocrinology clinic with the intention of initiating this therapy under close supervision. He was started on 54,000 IUs/day of vitamin D_3 (1,000 IUs/kg/day) and advised to follow a zero-calcium diet.

Following the initiation of this therapy, the patient reported significant improvement in his visual symptoms. After 2 years, his serum 25(OH)D and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] concentrations increased to above 400 ng/mL (reference range 30 – 100 ng/mL) and 180 pg/mL (reference range 18 – 64 pg/mL), respectively. At 4 years, serum 25(OH)D and $1,25(OH)_2D$ were 587 ng/mL and 496 pg/mL, while his serum calcium and parathyroid hormone levels remained within the normal range. He initially developed hypercalciuria, which later normalized upon adherence to a strict low-calcium diet. His serum creatinine and phosphorus levels remained normal throughout the follow-up period, ranging from 0.8 to 1.1 mg/dL and 2.8 – 3.8 mg/dL, respectively. **Figure 1B** demonstrates the patient's biochemical parameters after the initiation of high-dose vitamin D_3 therapy.

A repeated MRI approximately one year after the initial presentation revealed a stable FLAIR hyperintensity lesion in the left optic nerve. Thus far, he has not developed recurrence of symptoms up to 4 years after starting the therapy, and careful monitoring is ongoing.

Discussion

We present a case of optic neuritis and probable MS effectively treated with a high dose of vitamin D_3 at 1,000 IUs/kg/day, as recommended by Dr. Coimbra (6). The patient showed sustained symptomatic improvement of visual symptoms, along with radiological stability of the optic neuritis lesion after treatment. Our findings support the potential therapeutic benefits of this treatment approach. Importantly, although his serum 25(OH)D increased to the range that can typically result in vitamin D toxicity, he did not develop hypercalcemia due to strict adherence of zero-calcium diet (7). This underscores that careful monitoring of biochemical data and dietary counseling are important and feasible to minimize risks associated with this treatment.

The Coimbra group in Brazil claims the therapeutic efficacy of massive doses of vitamin D of 40,000-300,000 IUs/day to achieve serum 25(OH)D concentrations exceeding 400 ng/mL in various autoimmune disorders (8, 9). The probable mechanistic explanations for the therapeutic efficacy of vitamin D involve the immunomodulatory actions of $1,25(OH)_2D$ on T-helper cells, cytotoxic lymphocytes, NK cells and B cells (2). Another potential link between MS and vitamin D is evidenced by the increased risk of MS observed in individuals carrying certain genotypes of human leukocyte antigen (HLA) alleles, such as HLA-DRB1*1501 (10). Interestingly, the expression of the *HLA-DRB1* gene can be altered upon activation of vitamin D receptor (11).

It is important to note that long-standing ingestion of a very high dose of vitamin D of more than 50,000 – 100,000 IUs/day for months to years, resulting in serum 25(OH)D of more than 150 – 200 ng/mL, can lead to vitamin D toxicity. Vitamin D intoxication causes hypercalcemia, hyperphosphatemia, hypercalciuria, kidney stones, cardiovascular calcifications and nephrocalcinosis. This condition is one of the rarest medical conditions and is generally due to intentional or inadvertent intake of extremely high doses of vitamin D (as high as 1 million IUs daily for months to years) (7, 12-14). The primary underlying mechanisms of vitamin D toxicity

in causing hypercalcemia, hyperphosphatemia and hypercalciuria is increased activation of the vitamin D receptor in the intestinal epithelial cells, resulting in increased intestinal calcium and phosphate absorption. This leads to increased serum ionized calcium which in turn suppresses parathyroid hormone (PTH) production. The decrease in PTH causes a decrease in phosphate clearance resulting in hyperphosphatemia and an increase in renal calcium clearance (7). Therefore, adherence to a strict zero-calcium diet and close monitoring of biochemical parameters are crucial to mitigate the risk of toxicity associated with this mode of therapy.

Our case report has certain limitations. First, while the timing of visual symptom resolution and initiation of vitamin D therapy suggests a causal relationship, coincidence remains possible in a case report study. Additionally, it remains unclear how long the therapy should be continued. Finally, the safety of this mode of therapy has not been thoroughly investigated. Although we did not observe any evidence of vitamin D toxicity in this otherwise healthy 36-year-old man, no general conclusions can be drawn if this mode of therapy is safe in patients with underlying medical comorbidities.

Conclusion

Our case report highlights the potential therapeutic efficacy of high-dose vitamin D_3 treatment in managing optic neuritis and probable MS. The patient demonstrated sustained improvement in visual symptoms and radiological stability of the optic neuritis lesion without developing hypercalcemia. Further research is needed to elucidate the exact mechanisms, safety and efficacy of this treatment approach.

Conflict of Interest

Michael F. Holick receives grants from Carbogen-Amcis and Solius Inc is a consultant for Solius Inc., Ontometrics Inc. and Biogena and is a member of the speaker's bureau for Pulse LTD, Sanofi, Abbott and Menarini Inc. Nipith Charoenngam has no conflicts of interest.

Funding

None

References

1. Holick Michael F. Vitamin D Deficiency. New England Journal of Medicine.357(3):266-81.
2. Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020;12(7).
3. Moosazadeh M, Nabinezhad-Male F, Afshari M, Nasehi MM, Shabani M, Kheradmand M, et al. Vitamin D status and disability among patients with multiple sclerosis: a systematic review and meta-analysis. AIMS Neurosci. 2021;8(2):239-53.
4. Sintzel MB, Rametta M, Reder AT. Vitamin D and Multiple Sclerosis: A Comprehensive Review. Neurol Ther. 2018;7(1):59-85.
5. McLaughlin L, Clarke L, Khalilidehkordi E, Butzkueven H, Taylor B, Broadley SA. Vitamin D for the treatment of multiple sclerosis: a meta-analysis. Journal of Neurology. 2018;265(12):2893-905.
6. Lemke D, Klement RJ, Schweiger F, Schweiger B, Spitz J. Vitamin D Resistance as a Possible Cause of Autoimmune Diseases: A Hypothesis Confirmed by a Therapeutic High-Dose Vitamin D Protocol. Front Immunol. 2021;12:655739.
7. Holick MF. Vitamin D Is Not as Toxic as Was Once Thought: A Historical and an Up-to-Date Perspective. Mayo Clinic Proceedings. 2015;90(5):561-4.
8. Amon U, Yaguboglu R, Ennis M, Holick MF, Amon J. Safety Data in Patients with Autoimmune Diseases during Treatment with High Doses of Vitamin D3 According to the "Coimbra Protocol". Nutrients. 2022;14(8).
9. Finamor DC, Sinigaglia-Coimbra R, Neves LC, Gutierrez M, Silva JJ, Torres LD, et al. A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis. Dermatoendocrinol. 2013;5(1):222-34.
10. Alcina A, Abad-Grau Mdel M, Fedetz M, Izquierdo G, Lucas M, Fernández O, et al. Multiple sclerosis risk variant HLA-DRB1*1501 associates with high expression of DRB1 gene in different human populations. PLoS One. 2012;7(1):e29819.
11. Ramagopalan SV, Maugeri NJ, Handunnetthi L, Lincoln MR, Orton SM, Dyment DA, et al. Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D. PLoS Genet. 2009;5(2):e1000369.
12. Koutkia P, Chen Tai C, Holick Michael F. Vitamin D Intoxication Associated with an Over-the-Counter Supplement. New England Journal of Medicine.345(1):66-7.
13. Araki T, Holick MF, Alfonso BD, Charlap E, Romero CM, Rizk D, et al. Vitamin D Intoxication with Severe Hypercalcemia due to Manufacturing and Labeling Errors of Two Dietary Supplements Made in the United States. The Journal of Clinical Endocrinology & Metabolism. 2011;96(12):3603-8.

14. De Vincentis S, Russo A, Milazzo M, Lonardo A, De Santis MC, Rochira V, et al. How Much Vitamin D is Too Much? A Case Report and Review of the Literature. Endocr Metab Immune Disord Drug Targets. 2021;21(9):1653-9.

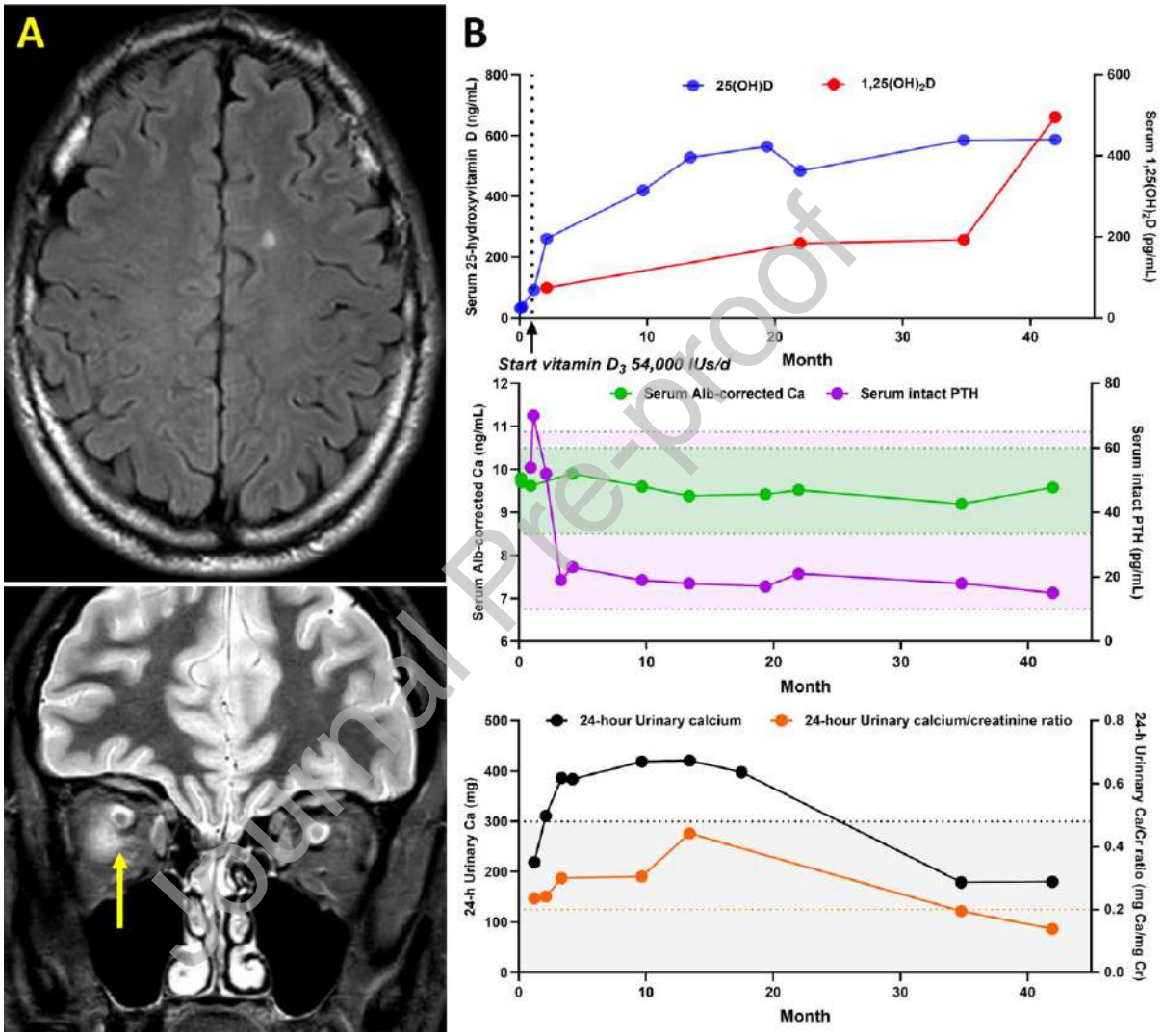


Figure 1 MRI brain and orbit demonstrating asymmetric T2 signal abnormalities in the left optic nerve (arrow) and T2 hyperintense white matter lesions (A) and the patient's biochemical parameters after ingestion of vitamin D_3 54,000 IUs daily (B)

Author contributions statement

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of this work.

Declaration of Conflict of Interest

Michael F. Holick receives grants from Carbogen-Amcis and Solius Inc is a consultant for Solius Inc., Ontometrics Inc. and Biogena and is a member of the speaker's bureau for Pulse LTD, Sanofi, Abbott and Menarini Inc. Nipith Charoenngam has no conflicts of interest.