Key Words: migraine, vitamin D serum levels, pregabalin, vitamin D restoring, inhibitory synaptic neurotransmission

Improved Efficacy of Pregabalin by Restoring Plasma Vitamin D Levels in Migraine: a Case Report

By Antonio Siniscalchi, Piergiorgio Lochner, Erika Cione, Adelia Michniewicz, Vincenzo Guidetti, Luca Gallelli

ABSTRACT: *Migraine appears to be the most common neurological syndrome in primary care. Pain in migraine is mediated by the release of inflammatory mediators at the level of nerves and blood vessels. The antioxidant and neuroprotective effects of vitamin D in the central nervous system suggest that deficiency of this vitamin can be involved in migraine. Moreover, low serum levels of vitamin D correlates with a higher incidence of chronic pain, including migraine and in co-administered with anti-migraine treatment reduces the frequency of migraine attacks.*

We report a 46-year old woman affected by migraine, anxiety and mild depressive mood (MSQ score: 24; BDI score: 34; VAS score: 8) that partially improved with pregabalin treatment (VAS: 5). Laboratory findings documented low serum levels of vitamin D (25-hydroxy-vitamin D: 12 ng/mL; normal range: 20–100 ng/mL; 1-25 di-hydroxy-vitamin D: 19 ng/mL, normal range: 25–66 ng/mL). The treatment with 10,000 UI vitamin D during pregabalin therapy induced an improvement of clinical symptoms (pain, anxiety and depression) and of the quality of life.

This case report suggest that in chronic migraine patient with anxiety and mild mood depression in treatment with pregabalin a supplementation of vitamin D improvement the clinical symptoms of migraine and a modulation of inhibitoy synaptic neurotransmission may explain this effect in our migraine patient. Psychopharmacology Bulletin. *2019;49(2):41–45.*

Introduction

The effectiveness of vitamin D is not only limited to the maintenance of bone integrity by regulating calcium homeostasis, but it is also known to possess apoptotic, anti-inflammatory and immunomodulatory properties.[1] Studies have shown the presence of enzymes involved in vitamin D metabolism as well as the

Siniscalchi, MD, Neurology Unit, Annunziata Hospital, Cosenza (Italy). Lochner, Department of Neurology, Saarland University Medical Center, Homburg, Germany. Cione, PhD, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria (Italy). Michniewicz, Biotechnologist, and Gallelli, MD, Department of Health Science, University of Catanzaro and Operative Unit of Clinical Pharmacology and Pharmacovigilance, Mater Domini Hospital, Catanzaro, Italy. Guidetti, MD, Department of Pediatrics and Child and Adolescent Neuropsychiatry, "Sapienza" University, Rome, Italy.

To whom correspondence should be addressed: Antonio Siniscalchi, MD, Clinical Specialist (Neurologist), Department of Neurology, Annunziata Hospital, Via F. Migliori, 1 - 87100 Cosenza, Italy. Tel: +39-0984-681351; Fax: +39-0984-21631; E-mail: anto.siniscalchi@libero.it

distribution of its receptors in all areas of the brain, suggesting that it acts as a neurosteroid with autocrine/paracrine properties[2] and its nutritional deficiency can induced an alteration of excitatory/inhibitory neurotransmission balance.[3] The pathophysiology of migraine is mediated by the release of inflammatory mediators around the nerves and blood vessels and the neuroprotective and antioxidant effects of vitamin D in the central nervous system suggest that deficiency of the steroid, as well as a modulation of inhibitory GABEergic neurotransmission,[4] can be involved in the pathogenetic mechanisms of migraine.[5] Few published data, report that vitamin D supplementation alone[1] and in co-administered with anti-migraine treatment reduces the frequency of migraine attacks.[6,7] We report a 46-year old woman with chronic migraine and treated with pregabalin (β-isobutyl-γ-Aminobutyric acid) with a partial control of symptoms that significantly improved after restoring plasma vitamin D levels.

Case Report

A 46-year old woman, with a history of smoking habit and hypertension in effective treatment with enalapril (20 mg/day), came to our attention in September 2016 for the worsening of migraine in term of pain and frequency (13 attacks/month in the last 6 months). She suffered of migraine attacks from the age of 16 year-old (frequency: one/two attacks/month) and used in a first time the non-steroidal antinflammatory drugs (i.e. nimesulide 100 mg or acetaminophen 500 mg as need), stopped for the development of skin rash and then amitriptyline (50 mg/day), stopped for the development of hypotension. In the last six years she used sumatriptan (50 mg/day).

Laboratory and instrumental tests excluded the presence of secondary headaches. The visual analogue scale of pain (VAS) documented a severe pain (VAS: 8).

Using the Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ), we documented an impaired quality of life (score 24/100) with the presence of anxiety. Using the Beck Depression Inventory-2 (BDI-2) scale we documented the presence of a mild depressive mood (score 29/63).

A diagnosis of primary headache type migraine without aura, according to ICDH III beta version, and the patient was discharged on pregabalin (Lyrica®, 150 mg/day); 1 week later, the persistence of pain (VAS: 8) induced the increase of pregabalin dosage (150 mg every 12 h). Two weeks later, the patient reported an improvement of pain (VAS: 5) with a decrease in the number of the attacks (from 13 attacks/month to 4 attacks/month) and with an improvement in either quality

of life (MSQ: 88) and mood depression (BDI-2: 9). About 1 week later pregabalin dosage was increased to 150 mg every 8 h (450 mg/day) with an improvement of pain in about 2 weeks (VAS: 3) but with the development of vertigo and sleepiness. Naranjo scale reported a possible association between pregabalin and adverse drug reactions (score 6), while high-performance liquid chromatography (HPLC) documented low levels of both, 25-hydroxy-vitamin D (12 ng/mL; normal range: 20–100 ng/mL) and 1-25 di-hydroxy-vitamin D (19 ng/mL; normal range: 25–66 ng/mL); the dosage of pregabalin was reduced to 150 mg every 12 h and a treatment with cholecalciferol (10,000 IU/week in single dosage) was started. A follow-up (January 2017) documented a significant decrease in both intensity (VAS: 2) and frequency (1 attack/month) of migraine. The HPLC evaluation documented a normalization in both 25-hydroxy-vitamin D and 1-25 di-hydroxy-vitamin D levels (25 ng/mL and 30 ng/mL, respectively). At the time of this paper, February 2016, the patient is on pregabalin (300 mg/day) and cholecalciferol was kept at maintenance dose of 1,000 UI/week in a single dose. She did not report worsening of the symptoms or development of adverse drug reactions.

Discussion

Here in, we report a woman with a chronic history of headache treated with NSAIDs and amitriptyline and then with sumatriptan who presented to our observation for a worsening of symptoms. Although anti-inflammatory drugs (NSAIDs) may be used as a first line of treatment,[8] their use could be often used in the acute phase, whereas their overuse may induce the development of side effects or chronic migraine.[8]

Therefore, in such condition, these drugs must be discontinued in patients with pain and anxiety, and a new treatment with amitriptyline or pregabalin is recommended.[7,9]

In our patient with a history of chronic headache, using MSQ and BDI-2 tests we documented a reduced quality of life and the presence of anxiety and depression.

The Antiepileptic drugs (AEDs) can be used in the treatment of chronic migraine.[9] Calandre et al.[9] in an open-label clinical study report that pregabalin, an AED that increase brain GABA levels,[10] may be an alternative to chronic migraine prophylaxis treatment.[9]

Moreover Arnold et al.[11] documented that pregabalin is able to act on pain, depression and anxiety without the development of side effects.

In this case, history documented the development of hypotension during the treatment with amitriptyline therefore we choose to prescribe pregabalin to chronic migraine prophylaxis treatment[7] with an effect

also on depression and anxiety.[10,11] Our patient with chronic headache, anxiety and depression partially improved after treatment with pregabalin, but at high dosage (450 mg/day) improved the pain, but induced the development of vertigo and sleepiness. Using the Naranjo probability scale, we documented a probable association between pregabalin and adverse drug reactions, therefore the dosage of pragabalin was reduced to 300 mg/day.

An association between lower plasma vitamin D levels and migraine was described[1] and a supplementation of vitamin D improvement the frequency of headache attacks in primary migraine,[1] although this data is controversial.[10] Recently, in a randomized, double-blinded, placebo-controlled clinical trial reported that a supplementation of cholecalciferol decrease the frequency of migraine attaks,[11] by a modulation of inhibitory neurotransmission.[3] A co-administered of vitamin D with anti-migraine treatment improved the attacks of headache.[7,8] We report that the supplementation of vitamin D during pregabalin treatment potentiates the effect of pregabalin in intensity and frequency of migraine. A synergic effect of increase GAbaergic inhibitory neurotransmission during supplementation of vitamin D in pregabalin treatment may explain this positive effect in our migrane patient. A chronic treatment with conventional AEDs with activity on cytochrome P450 hepatic enzyme, may have a negative influence on vitamin D metabolism,[14] but our patient started pregabalin, an AED without activity on cytochrome P450 hepatic enzyme, about 1 month before the administration of vitamin D.

However, up to date, not conclusive data were reported regarding the use of vitamin D supplementation in migraine because the correlation between serum level of vitamin D and migraine was not well evidenced in the clinical trials and criticisms are posed by experts in the field on the inclusion used criteria.[1,10] These different points of view could be due to many parameters influencing vitamin D homeostasis such as altitude, seasonal and individual differences (eg. gene polymorphisms in vitamin D receptors) not evaluated in the studies.[1,10]

However, prospective clinical trials or multicentre studies with a larger number of patients are necessary to confirm these observations in a larger group of patients. ✤

Conflicts of Interest and Source of Funding

We did not receive funding for this research and we have not conflict of interest.

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