

Bilateral Internuclear Ophthalmoplegia, Deficiency and High Dose Administration of Vitamin D in Pediatric-Age Multiple Sclerosis: A Pediatric Case Report and Review of the Literature

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Abstract

Oculomotor Disorders (OMDs) can be seen as the initial symptoms or during the course of multiple sclerosis (MS). Bilateral internuclear ophthalmoplegia (BINO) is a rare observation as clinical MS onset. BINO and its prognostic value in pediatric-age MS patients are not absolutely known. Vitamin D deficiency is thought to be associated with an increased disease activity in MS and vitamin D is supposed to be a potent immunomodulatory agent. Vitamin D deficiency, its probable effects on the disease pathogenesis, and high dose administration to a pediatric age patient presented with BINO are discussed in this report.

Keywords: Oculomotor disorders; Multiple sclerosis; Bilateral internuclear ophthalmoplegia Vitamin D; Immunomodulatory agent

Introduction

BINO in MS is thought to be related to the demyelination of the medial longitudinal fasciculi (MLF) [1]. BINO, its prognostic value and appropriate time of immunomodulation in this group of pediatric age MS patients are not well known.

Vitamin D deficiency and insufficiency are also thought to be related with MS [2]. Vitamin D treatment, regardless of vitamin D levels may have improving effects on pathophysiological mechanisms of MS. High dose administration of vitamin D for immunomodulation in MS in a pediatric-age patient is discussed in this report.

Case Report

A 15-year-old girl was admitted to the pediatric neurology department with the complaint of blurring of vision, visual confusion and a feeling of unsteadiness for almost two weeks. She had an adduction deficit in the right eye and nystagmus in the left eye on left gaze and an adduction deficit in the left eye and nystagmus in the right eye on right gaze (Video 1). Upward, downward, and primary gaze positions revealed nothing. Her tandem walking was seldom impaired. Her body mass index was: 20.5. Family and medical history revealed nothing.

Infectious parameters, vasculitis markers, and toxicology results revealed nothing. The lumbar puncture revealed that oligoclonal band was positive. The Ig G index was 1.64 (>0.6). The serum 25(OH) vitamin D level was 13 ng/mL (<20 ng/mL) in the deficiency range.

Magnetic resonance imaging (MRI) of the brain revealed T2 hyperintense nonenhancing lesions in the central pontine tegmentum, left superior cerebellar peduncle (Figures 1A and 1B); three deep white matter lesions and one additional enhancing lesion at the right side of the callosum splenium near the lateral ventricle (Figures 1C and D). A cervical and thoracic spine MRI revealed no additional intramedullary lesion. The lesions fulfilled Mc Donald revision criteria for MS regarding dissemination in time and space [3].

She received pulse steroid treatment for five days. At the end of the treatment her eye movements were normal. As our patient had vitamin D levels in the deficiency range, she was treated with the dosage of



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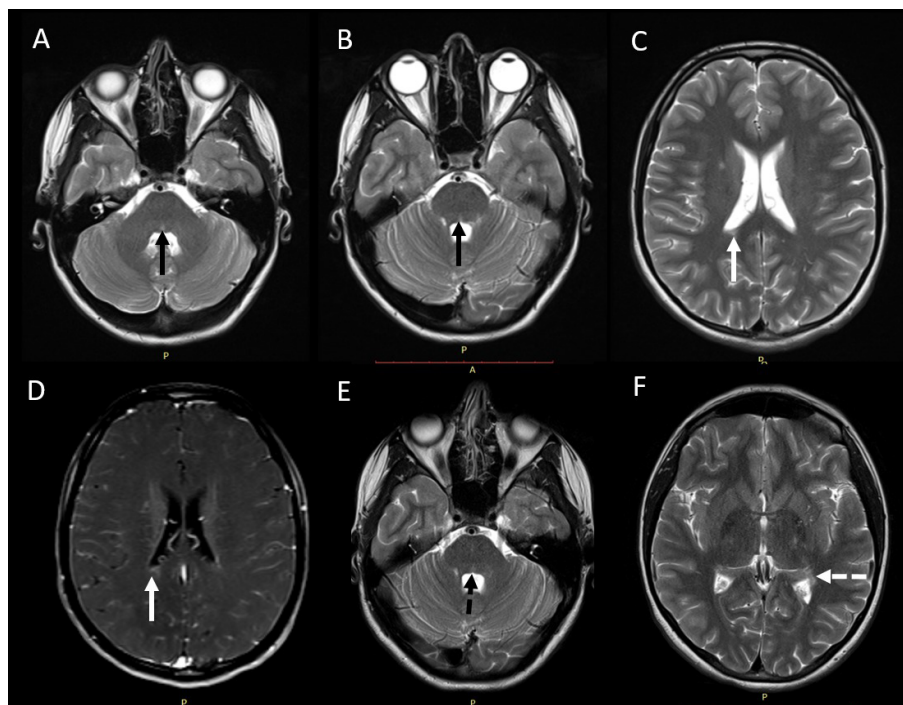


Figure 1: Axial T2-weighted (W) (TR/TE; 3500/100 ms) images at initial presentation show a T2 hyperintense lesion in the pontine tegmentum (black arrows; A, B) and another in the left superior cerebellar peduncle (B). In a higher section of T2-W and T1-W post-gadolinium spin-echo (TR/TE; 550/15 ms) images, an enhancing lesion appears in the left side of the corpus callosum splenium near the ventricle (white arrows; C, D). Three-month follow-up MRI shows fainting and disappearance of the pontine tegmentum lesion (dashed black arrow, E) and the left superior cerebellar peduncle lesions respectively (E). A new T2 hyperintense nonenhancing periventricular lesion appears at the left trigone level (dashed white arrow, F). Six months follow-up brain MRI showed no additional lesion.

800 IU/day D3 initially for two months. The checked level of 25(OH) vitamin D level was 12.8 ng/mL. The daily routine usage was strictly advised, and the checked level was 18 ng/mL in the control visit at the third month. This time she was admitted to the pediatric neurology department, with the complaint of feeling of unsteadiness, vomiting and vertigo for 5 days. A follow-up brain MRI in this second attack revealed disappearance of the left superior cerebellar peduncle lesion and fainting of the pontine tegmentum lesion (Figure 1E) with a new T2 hyperintense, but nonenhancing periventricular lesion near the trigone of the lateral ventricle (Figure 1F). She was advised a disease modifying drug (DMD) after this second attack and informed about the adverse effects of DMDs. She and her parents did not accept to use a DMD. A high dose D3 (2000 IU/day) was discussed and started with the consultation of pediatric endocrinology after an informed consent was taken before the treatment.

She has been using high-dose vitamin D for the last 18 months and she had no attacks since then. No adverse effects have been noted. The last measured level of vitamin D was 32 ng/ml. A follow-up at six month of the first and third month of the second episode on high dose vitamin D revealed no new T2 hyperintense or enhancing lesion as no clinical episode. A written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images.

Discussion

MS patients can present with OMDs during the course of the disease or sometimes as an initial symptom [1]. In a study of 150 patients with definitive MS and 13 patients with clinically isolated

syndrome, unilateral INO was found at a rate of 14.7% and BINO 4.9%, respectively [4].

Infratentorial MRI lesions were found in 76.8% of patients with OMDs [4], as seen in our patient. In a two year follow-up a group of patients with abnormal eye movements had a progression of EDSS score, supporting that the presence of OMDs may predict disability in MS [5]. A summary of literature about reasons of BINO is shown in Table 1.

Hypovitaminosis D is one of the most popular environmental risk factor for MS [6]. Vitamin D had improving roles on experimental autoimmune encephalomyelitis (EAE) [7]. Epidemiologically latitude, past exposure to sun, infections, smoking and the vitamin D serum level impact the risk of MS [8]. Our patient was a middle school student and her clothing style was available for sun exposure and she was not a smoker. She had no history of documented Epstein-Barr virus infection or parasites. She had only vitamin D deficiency as a triggering risk factor. The internationally accepted norms of vitamin D deficiency is defined as a 25(OH) vitamin D below 20 ng/ml and vitamin D insufficiency as a 25(OH) D of 21-29 ng/ml [9].

There are different vitamin D receptors in many parts of the body [10]; and probably in the MLF. We hypothesize that, hypovitaminosis D in the pathophysiological pathways of BINO in MS may be explained with that there could be vitamin D receptors in the MLF tractus.

Because TEM cells have been suggested to play a pathogenetic role in MS [11,12]; the effect of 1.25(OH)2D3 on T cell memory by culturing peripheral blood mononuclear cells from MS patients regardless of the serum values and healthy controls with vitamin D or

vehicles was studied. There was a reduction of the TEM cells in the vitamin D-treated cultures versus the vehicle-treated cultures [13].

The necessity of the routine usage of vitamin D regardless of calculated serum values is not absolutely known.

The appropriate vitamin D doses in MS patients are still confusing [14-16]. We administered 2000 IU/day dosage of vitamin D, firstly advised for a pediatric age MS patient in our center. She had no attack for the last 18 months and no adverse effect was seen. We believe that, if our patient did not use vitamin D for immunomodulation, the frequency and severity of the attacks might be more severe than expected. A review of the literature with high dose administration of vitamin D in multiple sclerosis is shown in Table 2.

Conclusion

BINO is a rare and can be the only clinical sign of MS onset. As in general, BINO is believed to be a high prognostic risk factor in the course of MS; high dose administration of vitamin D3 with the dosage of 2000 IU/daily in pediatric age is safe and may have improving roles on decreasing the frequency of relapses and severity of the disease.

Acknowledgement

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Conflict of Interest

None.

Author	Year of publication	Etiology
Rismonchi N et al.	2013	3 Boys (11,12,15 years of age) diagnosed with primary CNS tumours as pilomyxoid variant astrocytoma, anaplastic oligoastrocytoma, gliomatosis cerebri
Razavi ME et al.	2009	CO poisoning in a 8 year old girl
Akdal G et al.	2007	Vitamin B12 deficiency
Ozer F et al.	2005	15 Years old girl in persistant vegetative state due to diffuse axonal injury involving supratentorial and infratentorial structures and the splenium of CC
Tsuda H et al.	2004	Multiple sclerosis. 49 patients with ocular syptoms. Patients' age of onset varied from 17 to 51 years
Mimzeno-Alvarado AJ et al.	2002	SLE vasculitis. Case 2: 19 years old
Frohman EM et al.	2002	Multiple sclerosis 51/58 patients (88%) of patients had BINO
Muthukumar N et al.	2001	Trivial head injury 7 years old child presented with BINO following head injury
Shin M et al.	2000	3 Years old boy presented with aqueductal cyst causing intracystic high CSF pressure
Lagreze W D et al.	1996	Mesencephalic midline clefts
Kuroiwa T et al.	1993	Traffic accident trauma 18 years old boy presented with traumatic bilateral MLF syndrome
Mueller C et al.	1993	Minor occipital head trauma 6 year old boy presented with minor head trauma
Igarashi Y et al.	1992	Fisher's syndrome. 16 years old boy exhibited with BINO
Müri RM et al.	1985	Multiple sclerosis
Zak TA	1983	Benign episodic bilateral juvenile internal ophthalmoplegia. 9 years old girl.
Pryszmont M et al.	1982	Multiple sclerosis
Freeman JW et al.	1980	Craniopharyngioma. 15 years old girl
Lesser RL et al.	1979	Cryptococcal meningitis 17 years old girl with SLE had received prednisone and azathroprine , then devolped cryptococcal meningitis

Table 1: Literature reports of pediatric patients with BINO.

Author	Year of publication	Dosage and duration
Ashtari F et al.	2016	50.000 IU D3/every 5 days/3 months
Sotirchos ES et al.	2016	10.400 IU D3/daily/6 months
Rosjo E et al.	2015	20.000IU D3/week/96 weeks
Toghionifor N et al.	2015	50.000 IU D3/every 5 days/12 weeks
Bhargava P et al.	2014	50.000 IU D3/daily/96 weeks
Nystad AE et al.	2014	Cuprizone model Intraperitoneal 0.2 µg intraperitoneal calcitriol for 3 weeks
Golan D et al.	2013	4370 IU D3/daily/1 year
Steffensen LH et al.	2013	20.000 IU D3/weekly/96 weeks
Van Amerongen BM et al.	2012	6000 IU D3/daily/10 year
Dörr J et al.	2012	10.200 IU D3/daily/18 months
Knippenberg S et al.	2011	20.000 IU D3/daily/12 weeks
Kimball SM et al.	2011	4000-40.000 IU D3/daily/over 28 weeks followed by 10.000 IU/daily/12 weeks
Burton JM et al.	2010	4000-40.000 IU D3/daily/over 28 weeks followed by 10.000 IU/daily/12 weeks
Hiremath GS et al.	2009	50.000 IU/daily/7-10 days followed by 50.000 IU/weekly or biweekly for three months

Table 2: Literature reports of high dose administration of vitamin D in multiple sclerosis.

Informed Consent

All procedures followed were in accordance with local ethic committee in our institutions.

Animal Rights

This study does not contain any studies with animal subjects performed by the any of the authors.

Author Contributions

Dr. Genç Sel worked in the clinic, evaluated the patient, gathered the data, wrote and coordinated the manuscript. Dr. Altıaylık Özer contributed effort to ophthalmological evaluation of the patient. Dr. Aksoy and Dr. Dedeoğlu worked in the clinic. Dr. Savaş Erdeve contributed effort to endocrinological evaluation of the patient. Dr. Oğuz evaluated the serial neuroimaging findings of the patient.

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