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Calcium metabolism serum markers in adult patients with epilepsy and the effect of vitamin D supplementation on seizure control

Mario Tombini[a,*], Andrea Palermo[b], Giovanni Assenza[a], Giovanni Pellegrino[c], Antonella Benvenga[a], Chiara Campana[a], Anda Mihaela Naciu[b], Federica Assenza[a], Vincenzo Di Lazzaro[a]

[a] Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, University Campus Bio-Medico, via Álvaro del Portillo 21, 00128, Rome, Italy
[b] Department of Endocrinology and Diabetes, University Campus Bio-Medico, Via Alvaro del Portillo 21, Rome, 00128, Italy
[c] San Camillo Hospital IRCCS, Via Alberoni, Venice, Italy

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ABSTRACT

Purpose: To evaluate serum markers of calcium metabolism in adult patients with epilepsy (PWE) treated with antiepileptic drugs (AEDs) and the effect of vitamin D supplementation on seizure frequency.
Methods: Serum levels of calcium, phosphate, intact parathyroid hormone (iPTH) and 25-hydroxyvitamin D (25[OH]D) were compared in 160 PWE on chronic therapy with AEDs and 42 matched controls. Blood concentrations were analyzed taking into account the different features of epilepsy and treatment. Finally, the effect of vitamin D supplementation on seizure control was assessed in a subgroup of 48 drug resistant epileptic patients.
Results: PWE showed lower serum levels of 25[OH]D compared to control subjects ($p < .001$). Only 25% PWE showed normal 25[OH]D levels, whereas 41,9% had a vitamin D failure and 33,1% a vitamin D deficiency ($p < .001$). 25[OH]D serum levels depended on treatment duration, number of medications and enzyme-inducing AEDs ($p < .001$, $p < .001$, $p = .013$, respectively). Polytherapy and enzyme-inducing AEDs showed more detrimental effects on the 25[OH]D and calcium serum levels. The administration of vitamin D failed to significantly improve seizure control.
Conclusions: PWE show deficiency of vitamin D. The serum levels of 25[OH]D depend on the features and duration of AEDs treatment. Vitamin D administration in drug resistant epilepsy patients does not result in a reduction of seizure frequency.

1. Introduction

In the last few years the discovery of the systemic role of vitamin D has led to great interest in its functions in the modulation of physiological and pathological processes, as well as the prevention and treatment of many oncological [1], cardiovascular [2] and neurological diseases, such as dementia [3], Parkinson's disease [4], multiple sclerosis [5] and schizophrenia [6]. Vitamin D is metabolized to its hormonal form 1,25-dihydroxyvitamin D (calcitriol, 1,25[OH]2D) in various organs such as the gut and kidney and, in this form, it enters the brain via the blood brain barrier to act directly on cells containing its nuclear receptor, the vitamin D receptor (VDR) [7]. The neuroprotective role and involvement of vitamin D in the function of the central nervous system is supported by the presence in the brain of the enzyme 25[OH]D3-1a hydroxylase, which activates vitamin D, and by the expression of VDRs, especially in the hypothalamus and substantia nigra [8].The enzyme 25[OH]D3-1a-hydroxylase and nuclear VDRs are also present in the microglia, suggesting that vitamin D has both autocrine and paracrine effects on nervous system cells [9].

The hormonal form of vitamin D works as neurosteroids do and affects multiple intracellular metabolic pathways [10]. In the field of epilepsy, the studies have mainly focused on the effects of antiepileptic drugs (AEDs) on vitamin D metabolism and bone status. Vitamin D deficiency has high prevalence among patients with epilepsy (PWE), and compelling evidence suggests that AEDs are major risk factor for bone disease in adult PWE [11–13]. Early reports have focused on AEDs inducing the hepatic cytochrome P450 enzyme system which, in turn, increases vitamin D metabolism. This mechanism would eventually lead to secondary

* Corresponding author at: Neurology, Campus Bio-Medico University, Via Alvaro del Portillo 200, Trigoria, 00128, Roma, Italy.
E-mail address: m.tombini@unicampus.it (M. Tombini).

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Table 1
Clinical features of patients with epilepsy and control subjects.

	Patients with epilepsy [n = 160]	Controls [n = 42]	p
Sex [M/F]	62/98	15/27	n.s.
Age [y, mean ± SD]	50,6 ± 19,3	52,7 ± 19,4	n.s.
Epilepsy onset [y]	32,4 ± 23,5		
Duration of epilepsy [y]	17,5 ± 16,4		
Duration of AEDs [y]	15,7 ± 16 [min 6 months/max 63 years]		
Etiology of epilepsy	SFE 63/FEU 83/IGE 14		
Monotherapy/polytherapy N° of patients [%]	98[61,3%]/62 [38,8%]		
N° of AEDs median [range]	1 [min 1/max 5]		
EIAEDs/NEIAEDs, No of patients [%]	87 NEIAEDs [54,4%]/39 EIAEDs [24,4%] 34 EIAEDs + NEIAEDs [21,3%]		
Seizure free patients, No [%]	63 [39,3%]		
Seizure frequency (drug resistant epileptic patients) Median number of seizures/4 months [range]	4 [1–240]		

AEDs = antiepileptic drugs; EIAEDs = enzyme inducing antiepileptic drugs; NEIAEDs = non-enzyme inducing antiepileptic drugs; SFE = structural focal epilepsy; FEU = focal epilepsy of unknown etiology; IGE = idiopathic generalized epilepsy.

hypocalcemia and hyperparathyroidism [14,15]. Several other biological mechanisms would however make all types of AEDs potentially implicated in bone loss and disease [16].

Very few studies have addressed the relationship between vitamin D deficiency and epilepsy itself. An anticonvulsant effect of vitamin D is supported by animal investigations [17,18], but confirmed on patients with drug-resistant epilepsy in only two clinical reports. However, the very small sample size of these studies does not allow one to draw any definite conclusion [19,20].

The aims of our study were to evaluate serum markers of calcium metabolism (25-hydroxy vitamin D, parathyroid hormone, calcium and phosphate) in a large sample of adult PWE treated with different AEDs and to evaluate the effect of oral vitamin D supplementation on seizure frequency in a subgroup of drug resistant patients.

2. Materials and methods

2.1. Study population and experimental design

A cross-sectional cohort study was conducted in our Epilepsy Center from 2014 to 2016. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from all participants. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments.

We recruited epilepsy patients under chronic AED therapy (>6 months) and an age and sex-matched group of control subjects.

The exclusion criteria for patients and controls were: medical conditions affecting bone metabolism other than epilepsy, such as hepatic or renal disorders, hypothyroidism, obesity (body mass index >30 kg/m^2), malabsorption, history medications affecting calcium metabolism (e.g., vitamin A, anabolic steroids, bisphosphonates, glucocorticoids, thiazides, calcitonin, teriparatide) other than AEDs.

One-hundred-sixty Caucasian adult PWE (age: 50.6 ± 19.3 years; 98 females) and forty-two age and sex matched controls (age: 52.7 ± 19.4 years; 27 females) were enrolled (Table 1). All control subjects were Caucasian and were voluntarily enrolled among patients' relatives as they shared similar environmental conditions affecting vitamin D metabolism (e.g. diet, sunlight exposure).

On the basis of the neuroimaging data (CT scan and/or MRI), as well as the clinical and EEG features, 83 out of 160 patients were diagnosed as having focal epilepsy of unknown etiology, 63 as having structural focal epilepsy and the remaining 14 as having generalized idiopathic epilepsy. The structural focal epilepsy was due to: stroke/ischemic encephalopathy in 7 patients, non-paraneoplastic limbic encephalitis in 1, Temporal Lobe Epilepsy in 10 patients (4 patients with mesial sclerosis), post-traumatic encephalopathy in 12, cerebral hemorrhage in 3, perinatal encephalopathy in 8, Down Syndrome in 1, post-herpetic encephalopathy in 1, surgery for cerebral tumor in 10 patients (1 with oligodendroglioma, 1 with metastasis, 2 with astrocytoma, 6 with meningioma), suprasellar meningioma in 1, Alzheimer's Disease in 1, Progressive Myoclonic Epilepsy in 2, subependymal periventricular heterotopia in 1, cerebral cavernoma in 2, Arterio-Venous Malformations in 2, cerebral vasculitis in 1 patient. The seizure frequency was collected through clinical diaries that were kept by the patients and their caregivers. During the 4 months before study start (baseline period), 63 patients (39.3%) were seizure free; the median seizure frequency in 4 months in the remaining 97 patients was 4 seizures (range: 1–240). The patients' response to AEDs on the basis of etiology classification of epilepsy was displayed in Table 2. The type, number, dosage and administration schedule of drugs taken by the patients were recorded. Ninety-eight patients (61%) were on a single drug. The median number of AEDs used was 1 (range 1–5). The mean duration of antiepileptic treatment was 15.7 ± 16 years, ranging from 6 months to 63 years (Table 1).

AEDs were classified according to their effect on the cytochrome P-450 system [21]. Enzyme-inducing AEDs [EIAEDs] were: Phenytoin, Phenobarbital, Primidone, Felbamate, Oxcarbazepine, Topiramate >200 mg/day [22]. Non-enzyme inducing AEDs (NEIAEDs) were: Valproate, Lamotrigine, Gabapentin, Tiagabine, Pregabalin, Levetiracetam, Topiramate ≤200 mg/day, Ethosuximide, Vigabatrin, Acetazolamide, Piracetam, Clobazam, Clonazepam, Zonisamide, Lacosamide. Depending on their AEDs, patients were classified as "only EIAEDs", "only NEIAEDs", "both EIAEDs-NEIAEDs".

Thirty-nine (24.4%) patients were "only EIAEDs", 87 (54.4%) patients were "only NEIAEDs" and 34 (21.3%) patients were "both EIAEDs-NEIAEDs (Table 1).

Table 2
Patients' response to antiepileptic therapy on the basis of etiology classification of epilepsy.

Patients	FEU	SFE	IGE
Seizure free No of patients [%]	30 (36,1%)	25 (39,7%)	8 (57,1%)
Refractory epilepsy No of patients [%]	53 (63,9%)	38 (60,3%)	6 (42,9%)

SFE = structural focal epilepsy; FEU = focal epilepsy of unknown etiology; IGE = idiopathic generalized epilepsy.