Original Communication

Vitamin D status among patients with drug-resistant and non-drug-resistant epilepsy

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Abstract: *Background & Aims*: Epilepsy affects nearly 70 million people worldwide. Vitamin D deficiency may influence the balance of certain epilepsies. The purpose of this study was to determine the vitamin D status and anthropometric measurements of people with epilepsy (PWE), according to their pharmacosensitivity. *Methods*: Forty-six PWE, with or without drug resistance, underwent nutritional assessment after giving consent. Weight, body mass index (BMI), triceps skinfold thickness (TSF), fat mass (FM) and free fat mass (FFM) by bioelectrical impedance analysis were measured. Serum vitamin D was determined without supplementation. Deficiency was defined as a level < 30 ng/mL. Statistical analysis involved Student t test, ANOVA and Chi^2. *Results*: Patients were aged 44.5 ± 14.3 years, with 60.9% of drug-resistance. BMI was 28.7 ± 7.0, 2.2% were malnourished and 30.4% obese according to the BMI. The average vitamin D level was 15.3 ± 9.9 ng/mL, with 87.0% of deficiency, and 40.0% of severe deficiency (<10 ng/mL). The TSF was higher in drug-resistant cases (p = 0.03). There was no link between drug resistance and anthropometric measurements, FM, FFM or vitamin D concentration. Conclusions: Although limited in size, this study showed that PWE are more often obese. Vitamin D deficiency is more common than in the general population, with a much higher prevalence of severe deficiency.

Keywords: Vitamin D, anthropometric assessment, epilepsy, drug-resistance

Introduction

Epilepsy affects about 70 million people worldwide. Its prevalence is about 7.8 and 5.2/1000 population among men and women, respectively [1]. The drug resistance is defined as persistence of seizures despite trials of two anti-epileptic drugs (AEDs) as monotherapy and as a properly prescribed combination in response to the epileptic syndrome for at least two years. Its prevalence would be 20 to 30% [2].

Nutritional status can be impaired in people with epilepsy (PWE). Some treatments of epilepsy can modify the nutritional intakes. Indeed, some AEDs such as valproate and pregabalin, promote an increase of appetite. In contrast, other AEDs (felbamate, topiramate, zonisamide and stiripentol) can cause loss of appetite and thus promote the development of a state of malnutrition [3]. A state of malnutrition may also be responsible for deficiencies in micronutrients (minerals, trace elements, vitamins) with a role in neuronal function [3]. Vitamin D3 or 25-hydroxycholecalciferol (vitamin D), could also play a role in the balance of epilepsy. Vitamin D is involved in the regulation of neuronal growth factors (NT3, NT4, GDNF), and the synthesis of neurotransmitters. It may increase production of antioxidants such as glutathione, limiting the uptake of free radicals in neurons and having an inhibitory effect on neuronal calcium influx, thereby possibly limiting neuronal hyperexcitability [4]. Two studies in epileptic drug-resistant patients reported reductions of 30% and 40% in seizure frequency after supplementation with vitamin D [5, 6]. In animal models, injection of vitamin D into the hippocampus increased the seizure threshold [7], and mice deficient in the vitamin D receptor are more susceptible to seizures [8]. There is a relationship between certain AEDs and vitamin D deficiency that may reduce their effectiveness by lowering the seizure threshold [9]. Cytochrome P450 inducers (phenobarbital, phenytoin and carbamazepine) accelerate the catabolism of vitamin D. Furthermore,

cytochrome P450 inducers inhibit the 25-hydroxylation of vitamin D and its conversion to 1,25(OH)2 vitamin D (active form) [9, 10]. AEDs can also activate the pregnane X receptor (PXR), which, through induction of CYP24, promotes the conversion of 1,25(OH)2 vitamin D to its inactive liposoluble form [9]. The aim of this work is to describe vitamin D status and anthropometric measurements in a group of patients with epilepsy (PWE), both non-drug-resistant and drug-resistant.

Methods

The information used here is drawn from the database of the prospective study EPISTIGMA (Stigmatization of people with epilepsy; clinical trial: NCT01374204; ID: I09004) in 46 adult PWE followed in the Neurology Department of the University Hospital of Limoges. Eligible patients were aged at least 18 years and had a confirmed history of epilepsy of two years or more. They were defined as having stable epilepsy after two years without seizures. Otherwise, they were considered drug-resistant. After giving their informed consent, patients underwent nutritional assessment including measures of weight (kg), height (m), body mass index (BMI, kg/m^2), waist circumference (cm), skinfold thickness (mm): suprailiac, subscapular, biceps, triceps; mid upper arm muscle circumference (MUAMC, cm), brachial circumference (BC, cm), free fat mass (FFM, kg), fat mass (FM, kg) and determination of serum vitamin D (ng/ml). Weight was measured using an electronic scale (SECA^{TM}, Hamburg, Germany) and height was measured using a measuring rod in the upright position on a flat surface. BMI was calculated using the formula BMI = weight/height^2. Malnutrition was defined as BMI < 18.5, normal nutritional status as 18.5 $\leq$ BMI < 25, overweight as 25 $\leq$ BMI < 30 and obesity as BMI $\geq$ 30 [11, 12]. Waist circumference reflecting abdominal adiposity was measured using a tape measure, midway between the last rib and the iliac wing. Skinfolds, reflecting the FM, were measured on the right side using a Harpenden caliper (Baty International, Burgess Hill, UK). The measures chosen corresponded to the average of three successive measurements. The suprailiac skinfold was taken above the iliac crest on the anterior axillary line, the subscapular skinfold in an internal position in the tip of the scapula, the biceps skinfold was measured on the anterior surface of the arm midway between the acromion and olecranon, and the triceps skinfold (TSF) at the same level on the rear of the arm [11, 13]. The BC was measured at the same location as the TSF using a tape measure, and MUAMC, representing FFM was calculated using the formula: MUAMC = BC $-$ 0.314 $\times$ TSF [16]. FM and FFM were also obtained by Analycor® bioelectrical impedance (BIA) at 50 kHz (Eugédia, Chambly, France), hand-to-foot measurement in supine position for at least 5 minutes. FM and FFM were calculated according to the formulas provided. Vitamin D was measured by an immunological method: chemiluminescence (IDS-iSYS, IDS, Boldon, UK; Elecsys, Roche, Basel, Switzerland), electrochemiluminescence (Cobas 6000, Roche, Basel, Switzerland), enzyme immunoassay (ADVIA Centaur XP, Siemens, Saint Denis, France; LINK Diasorin, Saluggia, Italy), although the methods of vitamin D assay used were different, the threshold was the same for deficiency (<30 ng/ml). A concentration $\geq$ 30 ng/ml characterized normal status, $\geq$ 10–< 30 ng/ml, deficiency, and < 10 ng/ml severe deficiency [14]. No patient had received vitamin D supplementation.

Statistical analysis was performed using Statview 5.0 software (SAS Institute, Cary, NC, USA). Quantitative data are expressed as mean ± sd and qualitative data as a percentage. The tests used were the Student t test for comparison of quantitative data if two groups or ANOVA if more than two groups. We used the chi 2 test for the comparison of qualitative data. The significance level was $p < 0.05$.

Results

The study population had a mean age of 44.5 ± 14.3 years and a M/F sex ratio of 1.3; 60.9% were drug-resistant. The mean BMI was 28.7 ± 7.0 kg/m^2, with 2.2% (n = 1) of malnutrition, 39.1% overweight and 30.4% obesity. Anthropometric measurements were not significantly different according to the number of treatments (one, two or more than two), or with treatments that can cause weight gain and those that can cause weight loss.

The mean serum vitamin D was 15.3 ± 9.9 ng/ml, and 87.0% of patients were deficient. Deficiency was severe in 40.0%. The vitamin D level was higher, but not significantly, in patients given monotherapy compared to those taking multiple drugs (18.6 ± 10.8 ng/mL vs. 14.6 ± 9.9 ng/ml, p = 0.3).

Anthropometric data did not differ between patients with or without drug resistance. Only TSF was significantly increased when drug resistance occurred (28.6 ± 10.2 mm vs. 21.2 ± 11.3 mm, p = 0.03) (Table 1). Anthropometric measurements were not significantly different according to the level of vitamin D or to the presence of a vitamin D deficiency. Vitamin D status with or without drug resistance is shown in Figure 1. Mean levels of serum vitamin D were not significantly different in the two groups (14.8 ± 10.3 ng/ml vs. 16.1 ± 9.4 ng/ml, p = 0.7). The level of vitamin D or the percentage of vitamin D deficiency were not significantly different between patients with or without drug resistance. BMI, skin-fold thickness (except TSF) and body composition were not significantly different

Table 1. Nutritional criteria among patients with epilepsy with or without drug resistance

Criteria	Drug resistance (n = 28) (mean ± sd)	No drug resistance (n = 18) (mean ± sd)	p
Weight (kg)	82.5 ± 25.5	79.0 ± 17.6	ns
Body mass index (kg/m^2)	29.5 ± 7.6	27.3 ± 5.7	ns
Waist circumference (cm)	92.5 ± 19.4	93.5 ± 15.7	ns
Brachial circumference (cm)	33.2 ± 5.1	31.1 ± 4.7	ns
Triceps skinfold (mm)	28.6 ± 10.2	21.2 ± 11.4	0.03
Biceps skinfold (mm)	18.4 ± 10.2	11.7 ± 6.9	ns
Subscapular skinfold (mm)	24.4 ± 10.8	19.9 ± 8.6	ns
Supra-iliac skinfold (mm)	19.5 ± 9.9	16.6 ± 7.2	ns
Mid upper arm muscle circumference (cm)	24.2 ± 3.5	24.4 ± 2.8	ns
Free fat mass (kg)	56.5 ± 13.9	56.5 ± 10.5	ns
Fat mass (kg)	28.3 ± 16.4	20.2 ± 12.8	ns
Vitamin D concentration (ng/ml)	14.8 ± 10.3	16.1 ± 9.4	ns

Data expressed in mean with standard deviation (sd). ns: no significance.

between patients with or without drug resistance. 57.1% of women were drug-resistant versus 42.9% of men (p = 0.02).

At least one enzyme inducer (carbamazepine, oxcarbazepine, phenobarbital, phenytoin) was included in the treatment of 47.8% of patients, and 10.8% were receiving monotherapy. Four patients, 8.7%, were treated with two or more enzyme inducers. The vitamin D status of patients with or without enzyme inducers is shown in Figure 2. There was no significant difference in serum vitamin D in patients with or without enzyme-inducing treatment, either alone or in combination, or between different classes (non-barbiturate, barbiturate).

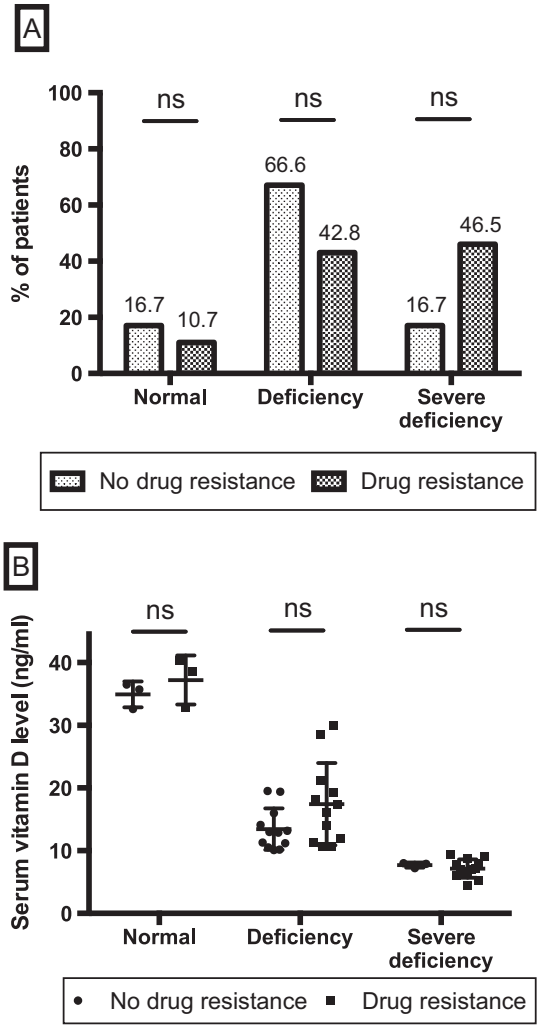

Figure 1. Vitamin D status (A) and levels of serum vitamin D (B) in epileptic patients with or without drug resistance. Clear column (A), dot (B): patient without drug resistance (n = 18); dark column (A), square (B): patient with drug resistance (n = 28). Vitamin D status: normal (≥30 ng/ml), deficiency (10≥ – <30 ng/ml), severe deficiency (<10 ng/ml). (B) Data with mean and standard deviation. ns: no significance.

Discussion

This study focuses on a small number of patients (n = 46), but is the first to provide information on the vitamin D status of adult PWE in France and, to our knowledge, only the second investigation of the anthropometric assessment of PWE in Western countries, after that of Elliott et al. in the United States [12]. Other studies have focused on nutritional status among people receiving a ketogenic diet or among children [15, 16]. A bias of our study was to use only the BMI to define malnutrition. Other malnutrition criteria such as the percentage of weight loss and the albumin assay were not assessed. The prevalence of malnutrition using the BMI is low in the current study (2.2%) but probably underestimated. This prevalence is close to the 4.0% reported by Elliott et al. [12]. The prevalence of excess of weight (overweight plus obesity) is high (69.5%), again close to the US study (59.0%), and significantly higher than in the general French adult population in 2012 (47.3%) [12, 17]. Although some treatments (carbamazepine, oxcarbamazepine, pregabalin, vigabatrin, clonazepam, sodium valproate) may promote weight gain, there was no relationship between these treatments and excess of weight [3, 18]. However, there were patients followed for more than two years, and therefore the weight gain might have occurred early after treatment initiation. In addition to iatrogenic treatment, reduced physical activity in PWE could also explain weight gain [19]. PWE might not accept weight gain, and thus not adhere to treatment associated with weight gain. Simple tracking of BMI and nutritional support associated with neurological care therefore seems important. In addition, obesity is likely to have the same deleterious

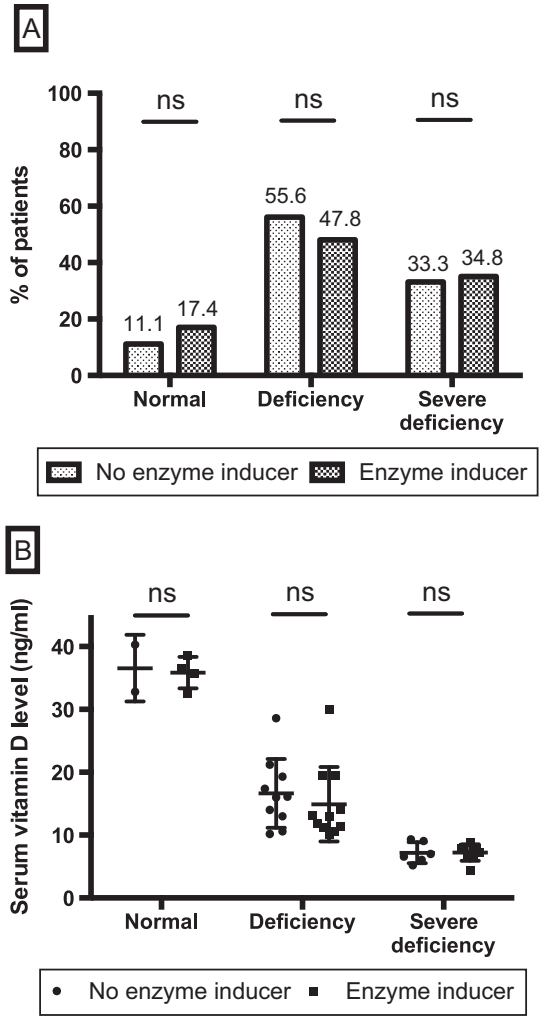

Figure 2. Vitamin D status (A) and levels of serum vitamin D (B) in epileptic patients with or without enzyme inducer treatment. Clear column (A), dot (B): patient without enzyme inducer treatment (n = 18); dark column (A), square (B): patient with enzyme inducer treatment (n = 23) (missing data = 5). Vitamin D status: normal (≥30 ng/ml), deficiency (10≥ – <30 ng/ml), severe deficiency (<10 ng/ml). (B) Data with mean and standard deviation. ns: no significance.

metabolic consequences, in terms of cardiovascular disease, cancer and poor quality of life, as it does in non-epileptic patients [20].

The prevalence of drug resistance (60.9%) was much higher than reported in France by Picot et al. (15.6%–22.5%) [1]. This is related to the methodology of inclusion of the EPISTIGMA study, which provides an equal proportion of stabilized and drug-resistant patients. The presence of drug resistance was not related to nutritional criteria. However, the TSF was higher in the case of drug resistance, which could be related to the fact that women were more often drug-resistant. Indeed, the TSF, representing FM, is typically higher among women than among men [21]. Additional analysis found a trend for a greater TSF in women PWE ($p = 0.07$) and a significantly lower FFM ($p = 0.04$).

In the population explored, the prevalence of vitamin D deficiency was slightly higher than in the French general population (87.0% vs. 80.1%) [22], but the mean serum concentration of vitamin D was much lower (15.3 ng/ml vs. 23.0 ng/ml), with 10 times more severe deficiency (40.0% vs. 4.0%) [22]. However, studies on epileptic children found less vitamin D deficiencies (between 59% and 63% of cases), but the thresholds for deficiency were different from ours (<32.0 ng/ml and < 29.0 ng/ml, respectively) with higher vitamin D concentrations (26.0–31.4 ng/ml) [23–25]. Drug resistant patients were no more deficient, although a role for vitamin D deficiency in drug resistance has been suggested [6]. The average concentration of vitamin D in patients with drug resistance was close to the study of Hollo et al. (14.8 ng/ml vs. 11.8 ng/ml) [6]. Patients treated with an enzyme inducer drug treatment had vitamin D concentrations close to those found by Mintzer et al. (15.7 ng/ml vs. 19.4 ng/ml [with oxcarbamazepine] and 20.4 ng/ml [with carbamazepine]) [26]. In our study, enzyme inducer drug was not associated with the presence or severity of vitamin D deficiency, despite its role in the degradation of this vitamin [10, 26]. However, our data do not indicate whether the deficiencies were linked to insufficient exogenous vitamin, a deficit in endogenous synthesis or enzyme inducer drug. Neither the phototype of the patient, nor the season when vitamin D was assayed were recorded in our study. Further study is needed. AED polypharmacy did not appear to lead to a higher prevalence of vitamin D deficiency, in contrast to the findings of Nettekoven et al. in children [27]. In view of the 40% of patients found to have severe deficiencies, and the consequent high risk of osteomalacia and osteoporosis, it seems important to assay vitamin D as part of monitoring and to start or modify supplementation as necessary depending on the assay results [10, 28, 29].

Conclusion

The patients group, although small, is sufficient to describe the vitamin D status and the anthropometric assessment of patients with epilepsy in France. Malnutrition is rare, but overweight is common and requires screening and careful management. Anthropometric measurements did not differ between patients with and without drug resistance. Vitamin D deficiency is more common than in the general population, with a much higher prevalence of severe deficiency, but is not related to drug sensitivity or the use of enzyme inducer drug. It appears to be important to supplement vitamin D in epileptic patients in order to reduce bone loss and lower the risk of fractures.

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Conflict of interest
All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

Statement of authorship
BG, JCD, PC, PMP conceived the study. BG, LP, FAL, OV, CM, LG carried out the studies. PJ, JCD carried out data analyses and performed the statistical analysis. PJ, BG, JCD, PC, PMP, PF drafted the manuscript. All authors read and approved the final manuscript.

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