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Evaluation of Serum Vitamin D level in Epileptic Children on Anticonvulsant Drug Therapy

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Abstract

Introduction: Epilepsy is widely regarded as the most common neurologic disorder in childhood. Two main groups of antiepileptic drugs are hepatic enzyme inducers that induce the hepatic P450 system and non-inducers. Nevertheless, non-enzyme-inducing AEDs can also be correlated with hypovitaminosis D; the mechanism for this needs to be investigated. Vitamin D deficiency, and thus impaired bone health, is known to be associated with hepatic CYP450 enzyme-inducing antiepileptic drug therapy and polytherapy, especially when used for extended periods.

Aim of the study: Evaluation of vitamin D in the serum of epileptic children on an anticonvulsant.

Subjects and Methods: Cross-sectional case-control research was performed on 90 children. It involved 45 cases of epilepsy on AEDs and 45 healthy control subjects. They were subjected to a full medical history, general and neurological examination, electroencephalography, vitamin D level, serum calcium, and phosphorus level.

Results: Twenty-four patients representing about 53.3% of all our cases who were on antiepileptic drugs for more than six months had vitamin D deficiency, compared to one healthy child representing about 2.2% who had vitamin D deficiency. We found that serum vitamin D levels were higher in patients who took AEDs for >1 year than those who were treated for a duration of 6 months to 1 year (57.1% vs. 40.0%).

Conclusions: Our data support that antiepileptic drugs that are used by children with epilepsy lead to a decrease in serum vitamin D, which is important for the homeostasis of calcium, phosphate, and magnesium. Its importance is essential to bone metabolism. Deficiency was more common in patients who took polytherapy for a long time.

Keywords: Epilepsy; antiepileptic drugs; vitamin D.

1. Introduction

Epilepsy is the most prevalent chronic neurologic disorder in children. It impacts between 0.5% and 1% of children [1]. Epilepsy is distinguished by the recurrence of
unprovoked seizures [2]. Epilepsy prognostic factors include the genesis of the condition, EEG abnormalities, the type of seizures encountered, the number of seizures that were present before therapy began, and inadequate initial responses to medication [3]. Vitamin D is a fat-soluble vitamin that plays an essential part in the metabolic processes that involve calcium and phosphorus [4]. Within the central nervous system, vitamin D plays a crucial role in the regulation of cell proliferation and differentiation, as well as neurotransmission and immunological responses [5]. Hypovitaminosis D is a disease that affects people all over the world. Hypovitaminosis D has been associated with factors such as gender, pubertal stage, skin pigmentation, the time of year that serum is collected, urban residence, geographical conditions (degree of latitude, etc.), obesity, chronic diseases (skin disease, malabsorption, cholestasis, renal insufficiency), and chronic medications (antiepileptic drugs and glucocorticoids) [6]. There are primarily two categories of medications used to treat epilepsy: those that stimulate the production of hepatic enzymes, such as carbamazepine, phenytoin, and topiramate, and those that do not stimulate the production of hepatic enzymes, such as clonazepam, levetiracetam, valproate, and zonisamide. When contrasted with non-inducers, enzyme inducers have the potential to have a more detrimental effect on bone mineral density (BMD) [7]. Vitamin D shortage is linked to the elevated hepatic metabolism of vitamin D, which in turn reduces intestinal calcium absorption, and this is especially true of long-term antiepileptic medication therapy and polytherapy [8]. Further research is needed to identify the mechanism linking non-enzyme-inducing AEDs to hypovitaminosis D. Children with epilepsy who use valproate have been shown to have reduced levels of 25-hydroxyvitamin D (25-OHD) and bone mineral density [9].

2. Subjects and methods

2.1. Subjects

Inclusion criteria

The age of children was 2–12 years old and had an epilepsy under AED mono or polytherapy for six months or more

Exclusion criteria

Patients with any hepatic, endocrinal, renal, or metabolic disorders (including cystic fibrosis and Crohn’s) were excluded. Patients who had vitamin D supplements less than six months before sampling were excluded as well.

2.2. Study design

This is a cross-sectional case-control research that aims to determine whether antiepileptic drugs affect serum vitamin D or not. This work was conducted from October 2020 to September 2021.
2.3. Statistical Analysis

Data analysis was performed using the statistical package for social science (SPSS 22.0).

3. Results

In this study, 90 patients were included in Group I, which included 45 patients with epilepsy who had been on anticonvulsants for more than 6 months. Group II (control group): It included 45 healthy children. The frequency of vitamin D deficiency was higher in patients treated for more than a year than in those treated for six months to one year (57.1% vs. 40.0%). The results showed no significant variation ($p = 0.197$). According to Figure 1, about 66.7% of cases are on monotherapy and 33.3% on polytherapy. 77.3% of cases on antiepileptic for more than one year, 22.7% of cases on antiepileptic for a duration of six months to a year.

Figure 1: Characteristics of antiepileptic (duration and number).

![Figure 1](image)

Figure 2 shows that 53.3% of cases have a deficiency of vitamin D compared to 2.2% of controls, 37.8% of cases have a normal vitamin D level compared to 77.8% of controls, and 8.9% of cases have an insufficiency of vitamin D compared to 20% of controls. As shown in Table 1, although the frequency of vitamin D deficiency was higher in participants treated with polytherapy than those treated with monotherapy (73.3% vs. 43.3%), it was not statistically significant ($p = 0.158$).
Figure 2: Vitamin D status in all participate children (N=90).

Table 1: The relation between Vitamin D status and treatment.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Deficiency</th>
<th>Insufficiency</th>
<th>Normal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=24)</td>
<td>(N=4)</td>
<td>(N=17)</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>13 (43.3%)</td>
<td>3 (10%)</td>
<td>14 (46.7%)</td>
<td>0.158</td>
</tr>
<tr>
<td>Polytherapy</td>
<td>11 (73.3%)</td>
<td>1 (6.7%)</td>
<td>3 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

In Figure 3, there was no significant relationship between vitamin D status and taking a sodium channel blocker or an inhibition calcium blocker ($p = 0.922$ and $0.399$, respectively).

While the occurrence of vitamin D deficiency was higher in patients treated for more than a year than those treated for 6 months to 1 year (57.1% vs. 40.0%), this variance was not significant ($p = 0.197$), as described above in Table 2.
Figure 3: Relation amongst vitamin D status and drugs type.

Table 2: Relation among vitamin D status and drugs duration in case group (N=45).

<table>
<thead>
<tr>
<th>Drugs duration</th>
<th>Deficiency (N=24)</th>
<th>Insufficiency (N=4)</th>
<th>Normal (N=17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12 months</td>
<td>4 (40%)</td>
<td>0 (0%)</td>
<td>6 (60%)</td>
<td>0.197</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>20 (57.1%)</td>
<td>4 (11.4%)</td>
<td>11 (31.4%)</td>
<td></td>
</tr>
</tbody>
</table>

4. Discussion

In children, epilepsy is the most common form of chronic neurological disease, affecting 0.5–1.0% worldwide [1]. Children are disproportionately affected by epilepsy. To maintain 70% of patients free from epilepsy, AEDs should be initiated as monotherapy [10].

Some fat-soluble compounds, including vitamin D, are called secosteroids. Parathyroid hormone [PTH] plays a crucial role in bone metabolism by regulating blood calcium levels through intestinal absorption of calcium and phosphate, an increase in osteoclast number, and the encouragement of appropriate PTH function [11]. Epileptic children have a higher chance of having weak bones and are also more likely to have other risk factors for vitamin D insufficiency [12].

Because of the numerous negative consequences that may result from children's continued use of AEDs, it is now recommended that their blood levels be monitored regularly and that they take vitamin D supplements. This is because children's continued use of these medications can create these problems [13].
Children treated with AEDs were known to have problems with bone metabolism that were two to three times the fracture risk of healthy controls [14].

The American Academy of Pediatrics recommended 400 IU to 1000 IU of vitamin D for children who had been treated recently for vitamin D deficiency [11].

Our research is one of the few reports to record the changes occurring in the levels of serum vitamin D in epileptic children throughout treatment with antiepileptic drugs. According to the findings of this study, 53.3% of epileptic children who were being treated with anti-epileptic medications had inadequate levels of vitamin D in their serum, whereas 2.2% of healthy people were found to have inadequate levels of vitamin D in their serum. Mridula et al. (2017) found results that were comparable to these [15]. Bhat et al. (2019) are another study of epileptic patients on antiepileptic drugs, which showed that 43.3% of cases had decreased vitamin D levels compared to 13.3% of healthy controls [16].

In our study, the mean level of vitamin D among cases was 48.9 and 70 among controls. However, in a study by Al-Taee et al. (2021), there was a significantly higher level of vitamin D3 in cases with epilepsy [17]. The rate of vitamin D deficiency in our study was 53.3% of cases, and the rate of vitamin D insufficiency was 8.9% of cases, whereas Saket et al. (2021) reported that about 10% of cases had vitamin D deficiency and 38.3% had vitamin D insufficiency [10]. Our study percentage was higher than that of Fong et al. (2014), who reported that 22% of cases had vitamin D deficiency and 41% of cases had vitamin D insufficiency [18]. In our work, vitamin D deficiency was noted, especially among cases who took sodium channel blocker antiepileptics like valproic acid. In the Mridula et al. (2017) study, vitamin D deficiency was most noted in patients who received carbamazepine as monotherapy [15]. There are differences in the prevalence of vitamin D deficiency from 4 to 75% in pediatric cases with epilepsy on AEDs, which have been reported in different studies [19]. There was a significant correlation between the length of time spent on antiepileptic medication and a drop in the 25-OHD level in the blood [13].

Final vitamin D levels were lower for individuals treated with antiepileptic medicines for more than a year in comparison to individuals administered with antiepileptic drugs for six months to less than a year. This result is similar to research by Kamili et al. (2020) [20]. However, this variance was not statistically significant. In Saleh et al.'s (2020) study, there was a substantial decrease in vitamin D levels among antiepileptic drug patients, and their follow-up revealed that prolonged duration of antiepileptic usage was connected with a significant reduction in vitamin D levels [11].

In our study, the prevalence of serum vitamin D deficiency was higher in cases treated with polytherapy than those treated with monotherapy (73.3% vs. 43.3%). This result is similar to Tosun et al. (2017) [21]. In Saleh et al. (2020), the occurrence of vitamin D deficiency among pediatric epilepsy individuals taking antiepileptic medications
was high, particularly in the polytherapy group [11].

Seizures, whether focal or generalized, did not affect serum vitamin D levels in our cases, and this study's findings support the notion that seizure type does not affect serum vitamin D levels. In Australia and Malaysia, cross-sectional studies of adolescents with epilepsy produced comparable results [22].

Our observation was supported by Mridula et al. (2017), who discovered that epileptic patients had substantially lower mean calcium levels than controls \((P = 0.016)\) [15].

Another longitudinal cohort study showed that patients with hypocalcemia had a higher prevalence of developing vitamin D deficiency as contrasted with those with normal and high calcium levels [23]. In their research on Indian epileptic children, Chaudhuri et al. (2017) found low Ca serum levels [24]. There was a significant connection between serum calcium and vitamin D; active calcium absorption decreases when serum vitamin D concentration decreases [20].

Hyperphosphatemia was observed in our study with a high significant mean level in epileptic patients in contrast to controls \((P<0.0001)\), which was opposite to Saket et al. (2021), which showed hypophosphatemia in 25.4% of cases and hypocalcemia in 24.4% of cases [10]. There was no significant variance amongst cases and controls as regards serum Ca and Ph in the Osman et al. (2017) study [25].

We also found that the prevalence of serum vitamin D level deficiency was high in patients treated with antiepileptic drugs for a long time, but this deficiency was not statistically significant. A similar result was found in the Toopchizadeh et al. (2018) study [26].

In this study, 71.1% of cases had generalized epilepsy and 17.8% had focal In Saket et al.'s (2021) study of convulsion types, 60% of all the cases were generalized tonic-colonic, followed by partial (23.3%) [10].

2.2% of patients in our study had normal EEG, and 97.8% had abnormal EEG in the form of subcortical epileptic activity (40%), focal focus (17.8%), brain insult (15.6%), and focal with secondary generalized (2.4%).

Normal EEG does not exclude epilepsy; in our study, around 2.2% of patients with normal EEG had epilepsy. But the study conducted by Abd El Naby and Naguib (2018) showed abnormal EEG in the epilepsy group (52%) [27].

Conclusion

Our data support that antiepileptic drugs that are utilized by children with epilepsy lead to a decrease in serum vitamin D, which is important for the homeostasis of calcium, phosphate, and magnesium. Its importance is essential to bone metabolism. Deficiency was more common in patients who took polytherapy for a long time.
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Ethical approval and consent to participate: The study was approved by the ethical committee of the Fayoum Faculty of Medicine. An informed written consent was obtained from all parents of the cases included in our research. The researcher briefed the parents on the objectives, examination, and investigation procedures of the study.

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Conflicts of Interest: All authors declare no conflict of interest.

References


