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Original Article

The hidden costs of seizure control: Metabolic and hormonal effects of anti-seizure medications in children

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ABSTRACT

Objective: This study aimed to evaluate the metabolic and hormonal effects of anti-seizure medications (ASMs) in children with epilepsy by comparing serum levels of vitamin D, calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), vitamin B12, folate, thyroid-stimulating hormone (TSH), and free thyroxine (fT4) between ASM-treated patients and healthy controls. A secondary aim was to investigate differences between patients treated with valproate (VPA) and those treated with levetiracetam (LEV).

Materials and Methods: A total of 106 pediatric epilepsy patients undergoing ASM therapy were included in the study, with 93 on monotherapy and 13 on polytherapy for at least six months. Additionally, 80 age- and sex-matched healthy controls were included. Serum biochemical parameters were analyzed retrospectively. Subgroup analyses compared patients on VPA and LEV monotherapy. Statistical comparisons and correlation analyses assessed relationships between drug exposure and biochemical values.

Results: Vitamin D levels were significantly lower in ASM-treated patients compared to controls ($p<0.001$). TSH levels were higher in the VPA group than in the LEV group ($p<0.001$), although there were no significant differences in thyroid hormone levels between ASM-treated patients and the healthy control group overall. No significant differences were observed in calcium, phosphorus, ALP, vitamin B12, or folate levels between the groups. The duration of ASM use was not correlated with any of the biochemical parameters.

Conclusion: Vitamin D deficiency and changes in thyroid function may occur in children treated with ASMs, especially VPA. However, vitamin B12 and folate levels tend to stay stable. Given the ongoing fluctuations in vitamin D and thyroid hormone levels, more frequent monitoring of these parameters may be warranted in pediatric epilepsy patients on ASM therapy. In contrast, less frequent assessment of vitamin B12 and folate may be enough unless there are clinical reasons to test further. More prospective studies are needed to determine the best monitoring approaches.

Keywords: Antiepileptic drug, children, folate vitamin D, thyroid hormones, vitamin B12

Introduction

Epilepsy is a chronic disorder characterized by recurrent, unprovoked seizures caused by abnormal electrical activity (1). Its prevalence is approximately 0.5–1%, making it one of the most common chronic illnesses in childhood (2). Seizure control may require long-term use of anti-seizure medications (ASMs), which have been shown in the literature to potentially affect thyroid function, bone health, and vitamin levels (3, 4). Sodium valproate (VPA) is a traditional ASM that has been used for many years to treat epilepsy (5), while levetiracetam (LEV) is considered one of the newer drugs that has become increasingly preferred for seizure control in recent years (6). Both medications are commonly used to manage epilepsy in the pediatric population. The primary aim of our study was to evaluate serum levels of 25-hydroxyvitamin D (25-OHD), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), vitamin B12, folate, thyroid-stimulating hormone (TSH), and free thyroxine (fT4) in children undergoing ASM therapy for epilepsy compared to healthy controls. The secondary aim was to examine the relationship between these vitamin and hormone levels among patients with epilepsy treated with either VPA or LEV.

Materials and Methods

The retrospective study was conducted between January 1, 2022, to February 1, 2023, involving children aged 1 to 18 years who visited the pediatric neurology outpatient clinic at Atatürk Sanatoryum Training and Research Hospital. A total of 106 children participated in the study, all diagnosed with epilepsy according to the definitions and classifications of the International League Against Epilepsy (ILAE) (7). These patients had no known chronic illnesses besides epilepsy and had been treated with either VPA or LEV, in monotherapy or polytherapy, for at least six months due to generalized or focal epilepsy. Furthermore, all participants had been seizure-free for a minimum of six months before enrollment. Of these, 93 children were on these medications as monotherapy, while the remaining 13 patients were also taking one or more additional ASMs, such as carbamazepine, clobazam, or other ASMs. Eighty healthy children, without any known chronic illnesses, and matched in terms of age and gender to the study group, were included as the control group in the study. Serum levels of 25-OHD (µg/L), P (mg/dL), ALP (U/L), Ca (mg/dL), vitamin B12 (ng/L), folate (µg/L), TSH (mU/L), and fT4 (ng/dL) in the children were retrospectively reviewed from the hospital's information management system records. Because this was a retrospective study, the exact timing of blood sampling in relation to ASM administration and diurnal variation could not be standardized; however, samples were obtained during routine outpatient visits in the morning hours (08:00–12:00) following the hospital's standard laboratory protocol. This condition should be considered when interpreting the results. Participants with chronic diseases other than epilepsy, those who had used ASMs for less than six months, individuals with clinical seizures during the follow-up period, those with known thyroid disorders or undergoing thyroid hormone replacement therapy, and individuals receiving vitamin B12, folate or vitamin D supplementation were excluded from the study.

The primary comparisons were made between children receiving ASM treatment for epilepsy and healthy controls. Secondarily, comparisons were conducted between 29 patients receiving VPA monotherapy and 57 patients receiving LEV monotherapy. Patients using carbamazepine, clobazam, or other treatments were excluded from the drug comparison analysis due to their small sample sizes. The demographic characteristics of the patients, along with their levels of 25-OHD, vitamin B12, folate, and thyroid hormones, were compared between groups. The levels of 25-OHD (30-100 µg/L), vitamin B12 (200-883 ng/L), folate (3.1-20.5 µg/L), fT4 (0.7-1.48 ng/dL), TSH (0.35-4.94 mU/L), Ca (9-11 mg/dL), P (4-9 mg/dL), and ALP (75-316 u/L) were considered within normal reference ranges. In the literature, vitamin D levels below 20 are considered deficient (8).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, version 30.0 software package (New York, USA: IBM Corp.). Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants. Continuous variables were presented as mean and standard deviation (SD), and categorical variables were expressed as frequencies and percentages. The data distribution normality was assessed with the Kolmogorov-Smirnov test and Shapiro–Wilk test. For comparisons between two independent groups, the Mann-Whitney U test was applied for non-normally distributed variables. To evaluate differences in serum levels of 25-OHD, Ca, P, ALP, vitamin B12, TSH, fT4, and folate between the epilepsy and healthy control group, independent sample tests were applied accordingly. Comparisons between patients on VPA monotherapy and those on LEV monotherapy were conducted similarly. Correlation analyses were performed using Spearman's correlation coefficients, depending on the distribution of data, to assess the relationship between the duration of anti-seizure medication use and serum levels of 25-OHD, Ca, P, ALP, vitamin B12, TSH, fT4, and folate. A p-value of less than 0.050 was considered statistically significant for all analyses.

Results

A total of 106 pediatric patients diagnosed with epilepsy (88 with generalized epilepsy and 18 with focal epilepsy; 53 males and 53 females) were included in the study. The mean age was 11.8±1.2 years (range; 1–18 years). In the control group, consisting of 80 healthy children (38 females and 42 males), the mean age was 11.3±3.2 years. The average duration of ASM use when blood sampling was 21.6±14.9 months among the patient group. Demographic characteristics are summarized in Table I. In children undergoing ASM treatment, the mean serum 25-OHD level was 12.5±5.1 µg/L, compared to 19.5±8.6 µg/L in healthy controls, with this difference being statistically significant ($p<0.001$). Among those on medication, the mean serum Ca level was 9.8±0.4 mg/dL, P level was 4.5±0.7 mg/dL, and ALP level was 201±90.9 U/L. In the healthy control group, these values were 9.8±0.5 mg/dL, 4.7±0.5 mg/dL, and 224.6

Table I: Demographic data of epilepsy patients and the control group

	Epilepsy Patients	Control Group
Number of total patients	106	80
Age (year)*	11.8±1.2	11.3±3.2
Gender†		
Girl	53 (50.0)	38 (47.5)
Boy	53 (50.0)	42 (52.5)
Epilepsy Type†		
Generalized	88 (83.0)	-
Focal	18 (17.0)	-
Medication used†		
Levetiracetam	65 (61.3)	-
Valproate	41 (38.7)	-
Carbamazepine	8 (7.5)	-
Clobazam	7 (6.6)	-
Other	3 (2.8)	-
Polytherapy†	13 (12.3)	-
Duration of medication (month)*	21.6±14.9	-

**: mean±SD, †: n(%), ‡: month± SD*

Table II: Laboratory values of epilepsy and control groups

	Epilepsy (n=106)			Control (n=80)			p†
	mean±SD	median (min-max)	IQR* 25-75	mean±SD	median (min-max)	IQR* 25-75	
Calcium (mg/dL)	9.8 ± 0.4	9.8 (8.8-10.8)	9.5-10.1	9.8 ± 0.5	9.8 (8.2-11.2)	9.5-10.1	0.526
Phosphorus (mg/dL)	4.5 ± 0.7	4.8 (3.2-6.0)	4.5-5.2	4.7 ± 0.5	4.8 (3.1-6.0)	4.4-5.1	0.752
Alkaline Phosphatase (U/L)	201 ± 90.9	175.5 (63.0-555.0)	140.5-250.8	224.6 ± 99.1	219 (5.9-592.0)	176.8-278.5	0.061
25-OH Vitamin D (µg/L)	12.5 ± 5.1	12.3 (3.5-27.0)	9.0-16.5	19.5 ±8.6	18.0 (6.1-61.0)	14.0-24.7	<0.001
TSH (mU/L)	2.44 ± 2.66	1.71 (0.41-25.78)	1.16-2.98	2.34 ± 1.48	1.96 (0.02-61.00)	1.23-3.20	0.655
Free T4 (ng/dL)	0.95 ± 0.14	0.96 (0.66-1.70)	0.87-1.03	0.95 ± 0.11	0.95 (0.65-1.20)	0.89-1.03	0.502
Vitamin B12 (ng/L)	347 ± 111	342 (140-634)	273-445	373 ± 139	355 (172-826)	280-414	0.347
Folate (µg/L)	8.2 ± 3.2	8.0 (2.1-12)	6.6-8.5	8.3 ± 2.7	8.2 (4-11.5)	7.6-9.0	0.481

***IQR:** Interquartile Range, †: Mann–Whitney U test*

Table III: Laboratory values of levetiracetam and valproate groups

	Levetiracetam (n=57)			Valproate (n=29)			p†
	mean±SD	median (min-max)	IQR* 25-75	mean ± SD	median (min-max)	IQR* 25-75	
Calcium (mg/dL)	9.7 7±0.42	9.8 (8.8-10.5)	9.5-10.1	9.82±0.46	9.8 (8.9-10.8)	9.5-10.1	0.704
Phosphorus (mg/dL)	4.75±0.67	4.8 (3.2-6.0)	4.4-5.3	4.63±0.58	4.7 (3.3-5.5)	4.5-5.0	0.334
Alkaline Phosphatase (U/L)	208.16±96.48	195 (63-555)	144-263	183.24±71.38	166 (71-328)	129-247	0.311
25-OH Vitamin D (µg/L)	13.11±4.6	12.3 (6.2-27.0)	9.2-16.5	12.71±4.74	12.1 (3.5-20.3)	8.3-17.1	0.833
TSH (mU/L)	1.66±1.09	1.35 (0.41-6.75)	1.02-2.12	4.07±4.39	3.19 (1.00-25.78)	2.09-4.35	<0.001
Free T4 (ng/dL)	0.97±0.14	0.96 (0.76-1.70)	0.87-1.04	0.93±0.12	0.95 (0.66-1.18)	0.86-1.02	0.346
Vitamin B12 (ng/L)	351.53±119.95	342 (140-634)	255-448	364.26±94.84	330 (217-621)	299-444	0.565
Folate (µg/L)	8.71±3.2	8.5 (6.0-12.7)	7.1-9.2	7.32±2.81	7.4 (3.4-10.1)	6.7-8.5	0.793

***IQR:** Interquartile Range, †: Mann–Whitney U test*

±99.1 U/L, respectively. There were no significant differences between the two groups in Ca, P, and ALP levels (p = 0.526, p = 0.752, p = 0.061, respectively). In our study, we also compared ALP values in patients with vitamin D levels below 20 between groups treated and not treated with ASMs. The ALP level was 202.5±92.8 U/L in the epilepsy group and 230.6±115.8 U/L in the control group; the difference was not statistically significant (p=0.090). TSH and fT4 levels were measured at 2.44±2.66 mU/L and 0.95±0.14 ng/dL, respectively, in the ASM-treated group, and 2.34±1.48 mU/L and 0.95±0.11 ng/dL in the control group. These differences were not statistically significant (p =0.655 and p =0.502, respectively). Similarly, the mean vitamin B12 level was 347±111 ng/L in the epilepsy group and 373±139 ng/L in the control group, with no statistically significant difference observed (p =0.347). The folate levels in the epilepsy and control groups were 8.2±3.2 and 8.3±2.7, respectively; the difference was not statistically significant (p= 0.481) (Table II). No significant correlation was found between the duration of medication use and the levels of vitamin D (p=0.612), vitamin B12 (p=0.920), folate (p= 0.54) or thyroid hormones (TSH p= 0.072, sT4 p=0.786). Correlations between medication duration and laboratory parameters were assessed using Spearman's rank correlation test due to non-normal data distribution.

Discussion

ASMs affect thyroid hormone levels through various mechanisms. Most increase the clearance of thyroid hormones by inducing hepatic microsomal enzymes, while others exert their effects via the hypothalamic-pituitary axis (9). It has been suggested that VPA may increase TSH levels due to its gamma-aminobutyric acid (GABA)-like effects.

GABA inhibits somatostatin release, which in turn suppresses TSH secretion; thus, reduced somatostatin activity may lead to increased TSH levels. Additionally, VPA might impair thyroid hormone production by causing zinc and selenium deficiencies. Magnesium deficiency may also contribute by reducing iodine uptake and thyroxine (T4) synthesis, thereby triggering increased TSH secretion. Furthermore, magnesium deficiency may reduce the physiological effects of thyroid hormones (10). VPA extensively binds to plasma proteins and may displace T4 from its binding sites, potentially altering circulating free hormone levels (11).

Several studies in the literature have shown that VPA can have variable effects on thyroid hormones. In line with our results, the survey conducted by Güngör et al. (12) reported elevated TSH levels in patients using VPA, without any significant alteration in fT4 levels (13). When examining studies on patients using VPA, while one study reported an increase in TSH levels along with a reduction in fT4, whereas another did not find significant changes in thyroid hormone levels (14-17). These varying results may be attributed to differences in methodologies and study populations across the respective studies. Moreover, some studies have also demonstrated that the duration of VPA treatment may influence thyroid function during therapy (18). However, in our study, no association was found between the duration of medication use and thyroid function.

LEV exerts its effects through synaptic vesicle glycoprotein 2A (SV2A), which is expressed in both the central nervous system and endocrine tissues. (19). However, in our study, no changes were observed in thyroid hormone levels in patients using LEV.

This finding is consistent with numerous studies in the literature, which include both short- and long-term treatment durations, where similar results have been reported (12, 15, 20, 21). In our study, although higher thyroid hormone levels were observed in the group treated with ASMs, no significant difference was observed in thyroid hormone levels between ASM-treated patients and the healthy control group. While a difference in thyroid hormone levels was observed between the groups using VPA and LEV, the lack of a significant difference between ASM-treated and non-ASM-treated patients overall may be attributed to the fact that the majority of patients in the ASM-treated group were receiving LEV, which doesn't affect thyroid function in our study.

ASMs may negatively impact bone health by decreasing bone quality and increasing the risk of fractures. This effect is thought to originate from disruptions in vitamin D metabolism, decreased osteoblast activity, and changes in collagen production (22). Many traditional ASMs, such as phenytoin, carbamazepine, and phenobarbital, act as inducers of the hepatic cytochrome P450 enzyme system, potentially leading to vitamin D deficiency (23). Widely used in children with epilepsy, VPA is not typically classified as a hepatic enzyme inducer; however, some studies have reported its ability to induce CYP3A4 and CYP24A1, enzymes involved in vitamin D catabolism (24). LEV is an ASM primarily metabolized through enzymatic hydrolysis of its acetamide group (27%), while the hepatic cytochrome P450 (CYP) system contributes only minimally (approximately 2.5%) (25). Despite its growing use in pediatric and adult epilepsy management, clinical evidence regarding its effect on vitamin D metabolism and bone health remains limited. Animal studies have provided some insight into the possible skeletal impacts of LEV. In a study by Nissen-Meyer et al. (26), LEV treatment in rats was linked to microstructural changes in the bone matrix, although bone mineral density (BMD) stayed the same.

Conversely, some experimental studies have found that long-term administration of LEV may lead to a significant decrease in bone mineral content in rat models, indicating potential adverse effects on bone quality with prolonged use (27). In the study by Vijayakumar et al. (28), patients receiving ASMs therapy exhibited significantly lower serum levels of 25-OHD, Ca, and P compared to the control group. In contrast, their ALP levels were significantly elevated. In the meta-analysis by Zhang et al. (29) evaluating the effects of ASMs on bone mineral metabolism, a decrease in 25-OHD levels was observed. Additionally, ALP levels increased, while no significant changes were found in Ca and P levels. In the study conducted by Yıldız et al. (30), which compared values before and after the use of ASMs, a significant decrease in vitamin D levels was observed, whereas no significant changes were observed in Ca, P, and ALP levels. The results of the study by Yıldız et al. (30) were consistent with ours. The presence of conflicting results in the literature regarding Ca, P, vitamin D, and ALP metabolism may be due to individual factors such as sun exposure, as well as underlying mechanisms that are not yet fully understood.

According to the Endocrine Society Guidelines, vitamin D levels should be monitored in children with epilepsy receiving ASM therapy, including those treated with VPA or LEV (31,32). Considering the high prevalence of vitamin D deficiency observed in our cohort, routine assessment of vitamin D levels should be included in the standard management of pediatric patients receiving ASM treatment.

Vitamin B12 levels in patients using ASMs remain a topic of debate in the literature. While some studies have reported decreased levels, others have found elevated or normal levels (4,33-37). Linnebank et al. (37) reported that, among patients receiving ASM monotherapy, neither the mean serum vitamin B12 levels nor the prevalence of subnormal vitamin B12 values differed significantly from those of untreated individuals or healthy controls. Notably, patients treated with valproate monotherapy exhibited higher mean serum vitamin B12 levels than untreated patients and controls, with this increase showing a dose-dependent pattern. In our study, as reported above, there was no significant difference in vitamin B12 levels observed between the groups that received and those that did not receive ASMs. However, unlike this study, we also found no significant difference in vitamin B12 levels between patients treated with VPA and those not treated with VPA. Conflicting findings in the literature on vitamin B12 levels may be attributed to differences in therapy duration, drug types used, dietary intake, or genetic factors that influence vitamin metabolism. Therefore, although our findings did not show a significant change in serum vitamin B12 levels, based on the data mentioned earlier, routine

monitoring of vitamin B12 levels in patients on long-term ASM therapy may be advisable. ASMs are known to impact folate metabolism, but the degree of this effect seems to differ based on the medication. VPA, a commonly used AED, has been associated with reduced serum folate levels in some studies. Sharma et al. (38) and Linnebank et al. (37) reported a significant decrease in folate levels in children receiving VPA therapy. On the other hand, several studies, including those by Geda et al. (39) and Özdemir et al. (40), found no significant changes in folate levels, suggesting that the impact of valproate may vary depending on factors such as dosage, treatment duration, and individual differences. LEV, a newer ASM, seems to have little to no impact on folate levels, as noted by Linnebank et al.(37). Reflecting these mixed results, our own study found no significant difference in serum folate levels between the ASM-treated group—most of whom were on LEV therapy—and healthy controls. These findings highlight that ASMs do not uniformly affect folate metabolism and reinforce the importance of personalized monitoring approaches in clinical practice.

Conclusion

In conclusion, while our study found that vitamin D levels and thyroid hormones were affected in children receiving ASMs, vitamin B12 and folate levels remained stable. However, previous studies in the literature have reported that each of these parameters can be influenced by ASMs. Considering our findings and the existing evidence, we suggest that clinicians stay alert to potential changes in these biochemical markers in children receiving ASM therapy, while emphasizing that our results are based on single-time-point measurements and do not allow for definitive recommendations on monitoring frequency. Nevertheless, given the ongoing fluctuations in vitamin D and thyroid hormone levels, more frequent monitoring of these parameters may be warranted. In contrast, vitamin B12 and folate levels could be assessed at longer intervals unless clinically indicated. Early detection and proper supplementation in deficiency cases are crucial, as they can help prevent long-term complications and support optimal growth and neurological development in children with epilepsy. Therefore, further studies are needed to determine the optimal duration and frequency of monitoring.

Limitations

The limitations of our study include neglecting confounding factors such as nutrition and age, measuring values at only one time point, the retrospective design, lack of standardization in the timing of blood sampling relative to ASM administration and diurnal variation, a small sample size, and limited diversity of treatment regimens. However, despite these limitations, the consistency of our findings with the literature indicates that our study group is homogeneous and that our data are accurate

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Atatürk Sanatoryum Training and Research Hospital (June 26, 2024, reference number: 2024 BÇEK/97).

Contribution of the authors

Study conception and design: ÖA, ANC, BD, ADB; data collection: ÖA, ANC, BD, AP; analysis and interpretation of results: ÖA, ANC, AP; draft manuscript preparation: ÖA, ANC, ADB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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