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Original article

Antiseizure medication effect-dosage on thyroid function in pediatric patients with epilepsy: Data analysis

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Abstract. *Background and aim:* The potential influence of antiseizure medications on thyroid function, leading to alterations in thyroid hormone synthesis and metabolism, has been previously reported. This study investigates the correlation between some commonly used antiseizure medications and their effects on thyroid hormones in pediatric patients. *Methods:* A retrospective analysis was conducted on 41 pediatric patients diagnosed with various types of epilepsy, receiving care at the Unit of Pediatric Clinic of the University Hospital Policlinico "G. Rodolico-San Marco" of Catania, Italy. Patients were categorized by epilepsy type, with a focus on the impact of the widely used antiseizure medication—valproate and levetiracetam—by assessing drug dosages, proportionally adjusted to body weight (pro/kg), in relation to thyroid-stimulating hormone (TSH) and free thyroid hormone (FT4) levels. *Results:* The results showed no significant linear correlation between drug dosages and thyroid parameters. This suggests that other factors, such as genetic predisposition, individual metabolic variations, and drug interactions, may contribute to thyroid parameter alterations in children receiving antiseizure medication. *Conclusions:* Further comprehensive studies are warranted to unravel the underlying mechanisms and effects of additional variables, which are essential for optimizing therapeutic approaches in pediatric epilepsy treatment. (www.actabiomedica.it)

Key words: antiseizure medication, thyroid, epilepsy, children

Introduction

The causes of epilepsy are diverse and mainly related to structural, genetic, infectious, metabolic, autoimmune, and unknown conditions (1-3). Antiseizure medications (ASMs) are categorized into different generations based on their market introduction and pharmacological characteristics. Each generation presents specific advantages and limitations in treating epilepsy (4). Treatment for pediatric epilepsy differs from that for adults due to the dynamic development and maturation of the brain during childhood. The administration of ASMs in children hinges upon several determinants, including the child's age, type of epilepsy, severity of the disorder, and the individual response to medication. The primary goal is to achieve optimal seizure control with minimal dosage and, ideally, with a single medication. However, ASMs treatment may pose risks for various adverse effects on different organs and systems (5-9). In epileptic children, studies on the impact of ASMs on thyroid function have shown controversial results. Verrotti et al. (10)

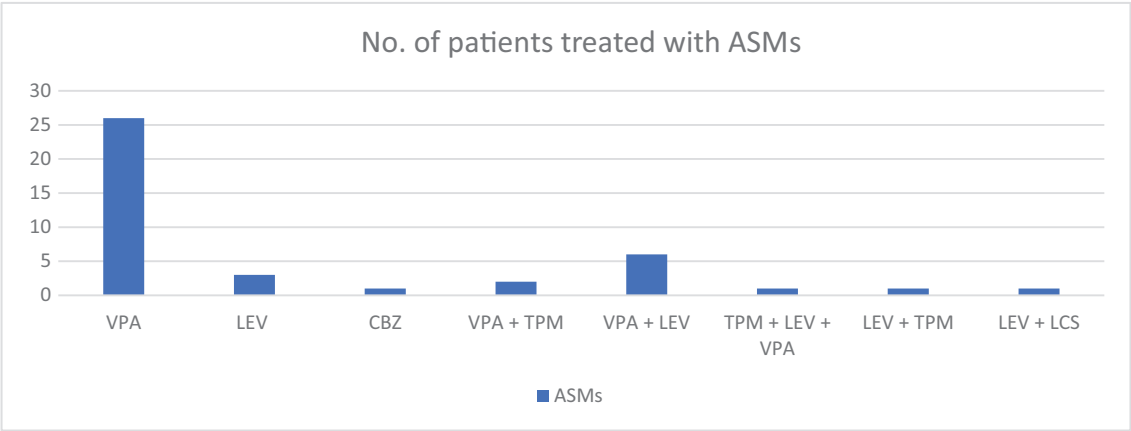

Figure 1. The x-axis represents the administered ASMs, both in monotherapy and in combination, while the y-axis shows the number of patients who received specific ASMs.

and de Vries et al. (11) found no thyroid hormone anomalies in children treated with valproate (VPA) monotherapy, while Goldberg-Stern et al. (12) reported no adverse effects on body weight, metabolism, or endocrine function. However, other studies have shown thyroid dysfunction and subclinical hypothyroidism in young epileptic patients treated with VPA and others ASMs (13-18). Subclinical hypothyroidism denotes a condition in which there are minor deviations in thyroid hormone levels, though patients do not exhibit clear symptoms. This is characterized by slightly elevated thyroid-stimulating hormone (TSH) levels while free thyroxine (FT4) values remain within normal limits (19-22). Mild symptoms such as fatigue, weight gain, dry skin, and reduced concentration may occur (20-23). This condition represents an early phase of thyroid insufficiency, requiring careful monitoring and management. In clinical practice, comprehending the potential impact of ASMs on thyroid function in pediatric epileptic patients is of critical importance. This study aims to investigate the correlation between ASMs and thyroid dysfunction, including subclinical hypothyroidism, in this population. Furthermore, this study attempts to point out the factors that may influence thyroid function, thus guiding more precise and individualized therapeutic approaches. Considering the frequent subtle or absent symptoms in children, regular monitoring of TSH and FT4 levels is essential to promptly identify any disturbances in thyroid function.

Material and Methods

A retrospective study was conducted from 2001 to 2024, involving 41 pediatric patients diagnosed with various types of epilepsy and actively undergoing ASMs treatment. Patients were selected from the Unit of Pediatric Clinic of the University Hospital Policlinico "G. Rodolico-San Marco" of Catania, Italy. Patients were categorized based on the type of epilepsy, including generalized and focal epilepsies, specific epilepsy syndromes, and epileptic encephalopathies.

Statistical analyses were performed using STATA/SE 18.0 version. Descriptive statistics, including mean, standard deviation, and range, were computed to summarize the age distribution. Information on whether any family members had a history of thyroid disorders was collected through patient history records. The Body Mass Index (BMI) was calculated for all patients using their height and weight at the time of thyroid function assessment. A correlation analysis between BMI and thyroid parameters (TSH and FT4) was conducted to explore any possible associations. The presence of Antithyroglobulin (anti-Tg) and Antiperoxidase Antibodies (anti-TPO) was evaluated, particularly in

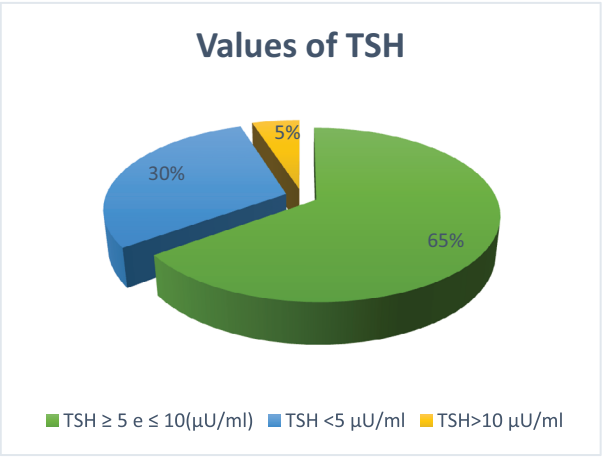

Figure 2. Cohort of epileptic patients divided into three groups based on TSH levels following the administration of ASMs.

patients with elevated TSH levels, to assess potential autoimmune thyroiditis. For patients with TSH levels above 10 µIU/L, thyroid ultrasounds (US) were performed to detect any structural abnormalities indicative of underlying thyroid pathology. An analysis of drug dosages, expressed as a ratio to each individual's body weight (per kg), was conducted, and these values were subsequently correlated with TSH and FT4 levels in the patient's cohort. The levels of TSH and FT4 were measured using chemiluminescent immunoassay (CLIA) techniques on serum samples, normal values were respectively 0,34 - 4,2 µIU/mL and 6,8 – 16 pmol/L. The intra-assay and inter-assay coefficients of variation for FT4 and TSH were also assessed. A Pearson correlation analysis was conducted to assess the linear relationship between VPA and LEV dosage pro/kg of body weight and the thyroid markers TSH and FT4 (Figure 2).The correlation coefficients were calculated to determine the strength and direction of the association between these variables. A significance level of $p < 0.05$ was considered for the interpretation of the results (Figures 3-6).

Children were followed up with a comprehensive assessment, considering dosage per kg and patient age. The monitoring period for each patient, from the start of ASMs to the emergence of abnormal TSH/FT4 values, was recorded to evaluate the mean follow-up duration and identify any diversities in the onset of any thyroid functional alterations. Data collection was conducted after obtaining written informed consent from the families, in full compliance with the Declaration of Helsinki.

Results

The mean age of the 41 patients was 11.81 years (SD = 4.51), with ages ranging from 3.7 to 18.3 years. Among the 41 patients, 16 were female (39,02%). The majority of patients were diagnosed with generalized epilepsy (56%), followed by focal epilepsy (17%), epilepsy syndromes (15%), and epileptic encephalopathy (12%). VPA was the most frequently prescribed medication, either as monotherapy or in combination with other ASMs (Figure 1). Among the 41 patients, 12% (5/41 patients) had a positive family history of thyroid dysfunction. There was no significant correlation between family history and alterations in TSH ($p = 0.52$) or FT4 ($p = 0.64$), suggesting that genetic predisposition did not play a major role in the observed thyroid changes. The mean BMI for the cohort was 18.5 kg/m² (range: 14.5–24.0 kg/m²). BMI was weakly correlated with TSH (correlation coefficient $r = 0.21$, $p = 0.18$) and FT4 ($r = -0.19$, $p = 0.22$), indicating no significant association between BMI and thyroid function in this population. Patients with elevated TSH (≥ 5.0 µIU/L) did not have higher BMIs compared to those with normal TSH levels ($p = 0.45$). Antithyroid antibodies were tested in 20/41 patients, of whom 15% (3/20 patients) were positive for anti-Tg and 10% (2/20 patients) were positive for anti-TPO. All patients with elevated TSH (≥ 5.0 mIU/L) tested negative for both anti-Tg and anti-TPO, suggesting that autoimmune thyroiditis was not a primary contributor to thyroid dysfunction in this cohort. Thyroid US was performed on 5 patients with TSH levels greater than 10 µIU/L. None of the patients showed significant structural abnormalities, with only 1/5 of patients having a mildly enlarged thyroid gland (thyroid volume at the 90th percentile for age). These findings indicate that elevated TSH in this subset of patients was unlikely due to structural thyroid disease.

The intra-assay and inter-assay coefficients of variation for FT4 and TSH were 5.93% and 1.00%

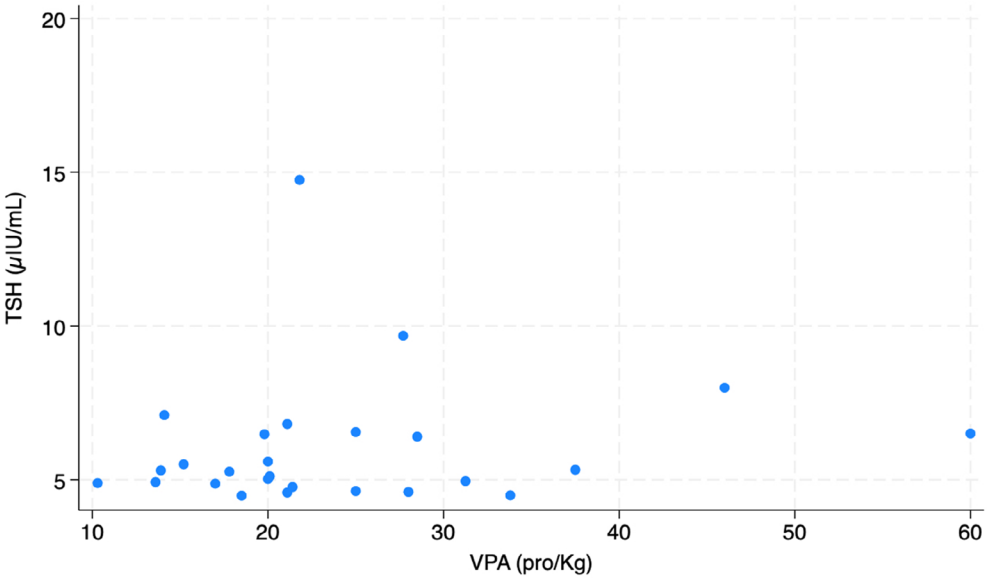

Figure 3. Scatter plot illustrating the relationship between VPA dosage pro/Kg of body weight (x-axis) and TSH levels (y-axis) in a cohort of pediatric patients with epilepsy. Each point represents an individual patient, and the distribution of data shows a weak positive correlation between VPA dosage and TSH levels, with no clear linear trend observed in the cohort.

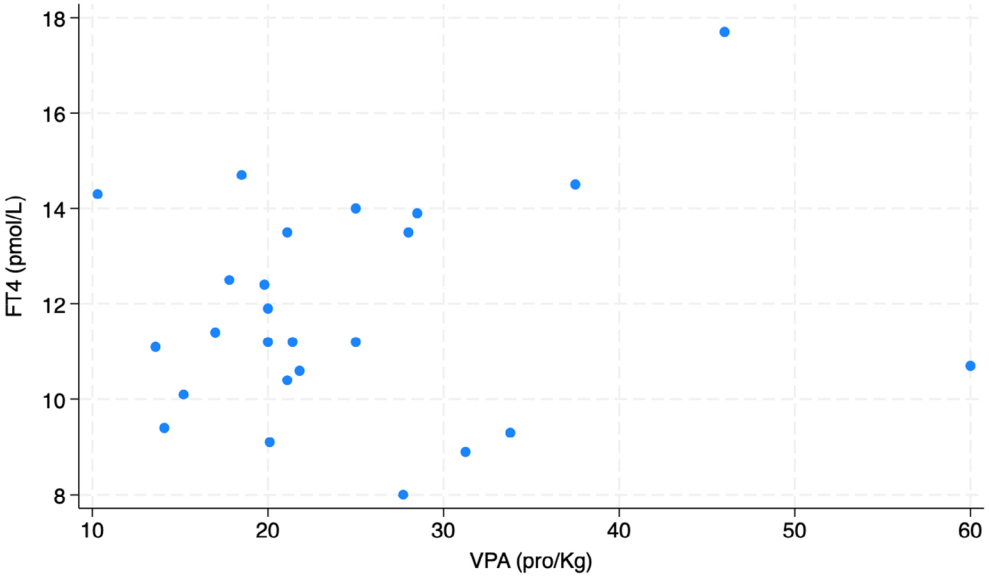

Figure 4. Scatter plot depicting the relationship between VPA dosage pro/Kg of body weight (x-axis) and FT4 levels (y-axis) in pediatric patients with epilepsy. Each point represents an individual patient. The plot shows a weak positive correlation between VPA dosage and FT4 levels, with no clear linear pattern observed in this sample.

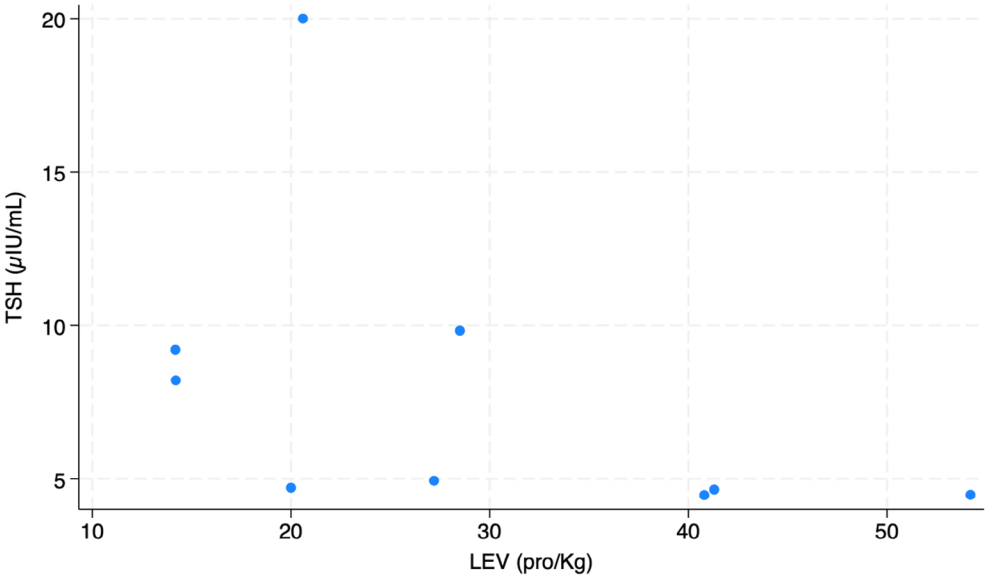

Figure 5. Scatter plot illustrating the relationship between LEV dosage pro/Kg of body weight (x-axis) and TSH levels (y-axis) in a cohort of pediatric patients with epilepsy. Each point represents an individual patient. The data suggests a moderate negative correlation, with higher LEV dosages potentially associated with lower TSH levels, though the relationship is not strongly linear and the sample size is small (n=9).

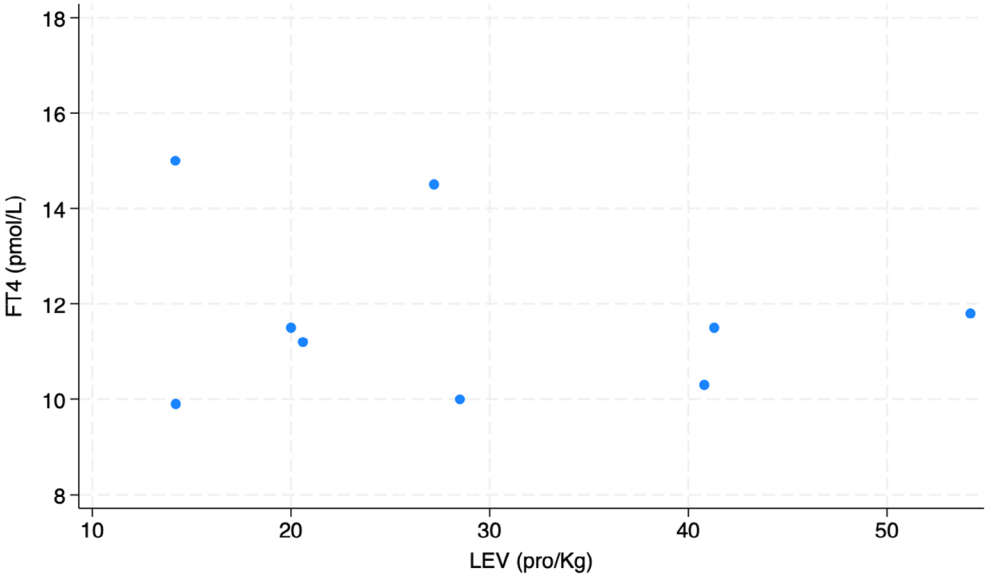

Figure 6. Scatter plot showing the relationship between LEV dosage pro/Kg of body weight (x-axis) and FT4 levels (y-axis) in a cohort of pediatric patients with epilepsy. Each point represents an individual patient. The plot indicates a weak negative correlation between LEV dosage and FT4 levels, with minimal evidence of a strong linear association in this sample, though the relationship is not strong since the sample size is small (n=9).

for FT4, and 5.68% and 7.89% for TSH, respectively. The correlation analysis between VPA dosage pro/kg of body weight and TSH levels revealed a very weak positive correlation (r = 0.13, n = 26). Similarly, the correlation between VPA_pro/Kg and FT4 levels showed a weak positive correlation (r = 0.15, n = 25). Both correlation coefficients indicate a minimal linear relationship between VPA dosage and thyroid function parameters, suggesting that VPA dosage has little to no significant impact on TSH and FT4 levels in this sample, (Figures 3-4).

The Pearson correlation analysis between LEV_(pro/Kg) and TSH levels showed a moderate negative correlation (r = -0.46, n = 9), suggesting that higher doses of LEV may be associated with a slight decrease in TSH levels. However, the correlation between LEV_(pro/Kg) and FT4 levels revealed a weak negative correlation (r = -0.18, n = 9), indicating little to no meaningful relationship between LEV dosage and FT4 levels. Given the small sample size, these results should be interpreted with caution and warrant further investigation with larger datasets (Figures 5-6).

Discussion

The findings of this study indicate that factors like family history, BMI, antithyroid antibodies, and structural abnormalities are not strongly associated with the observed thyroid function changes in this cohort. Furthermore, the results show that both VPA and LEV administration do not have a strong or significant correlation with thyroid function parameters (TSH and FT4) in pediatric patients with epilepsy. The correlation analysis between VPA pro/Kg and TSH levels revealed a very weak positive correlation (r = 0.13, n = 26), while the correlation with FT4 showed a similarly weak positive association (r = 0.15, n = 25). These results suggest that VPA dosage has little to no significant impact on TSH and FT4 levels in this cohort. Similarly, the analysis of treatment with LEV in a smaller subset of patients (n = 9) demonstrated a moderate negative correlation with TSH levels (r = -0.46), indicating that higher LEV dosages might be associated with a decrease in TSH. However, the correlation between LEV and FT4 levels was weak (r = -0.18), suggesting that LEV has minimal impact on FT4 levels in this population. These findings align with previous studies, such as those by Verrotti et al. (10), which reported no significant thyroid function changes with VPA therapy in children. However, other studies, like those conducted by Kim et al. (13), have suggested that VPA therapy may lead to subclinical hypothyroidism, particularly at higher doses, showing conflicting results in the literature. The inconsistency in the findings emphasizes the need for further investigation into individual factors that could contribute to these variations, such as genetic predisposition, metabolism, and potential drug interactions. Furthermore, a clinical study involving 90 adult males with epilepsy showed that those using carbamazepine (CBZ) or oxcarbazepine (OXC) had reduced serum T4 and FT4 levels, while T3 and TSH levels remained within normal range. Conversely, those using VPA had normal thyroid hormone and TSH levels (24). Aygun et al. (25) found no significant differences in average FT4 and TSH levels in children treated with various ASMs, including VPA, phenobarbital (PB), CBZ, OXC, LEV, and topiramate (TPM). However, children on VPA exhibited a notable decrease in FT4 levels throughout the treatment period, followed by a significant and gradual increase in TSH levels after the ninth month, although TSH levels remained within normal limits. The results of this study are consistent with those of Shi et al. (26), who found no significant adverse effects of LEV monotherapy on thyroid hormone levels in children with epilepsy over a 12-month period. This result suggests that LEV treatment may not significantly affect thyroid function in paediatric patients with epilepsy. Similar findings were reported by Nishiyama et al. (27), and Yilmaz et al. (28) who found no significant changes in FT4 and TSH levels during LEV treatment. In contrast, a study by Elshorbagy et al. (29) comparing traditional and newer ASMs observed a significant reduction in FT4 levels and an increase in TSH among children treated with traditional ASMs. Children treated with newer ASMs showed no significant changes in FT3, FT4, or TSH levels compared to the control group. These conflicting results highlights the importance of considering additional variables, such as individual drug sensitivity, metabolism, and possible drug interactions when evaluating the relationship between ASMs and

thyroid function. Further studies involving larger samples sizes and longer-term follow-up are necessary to better understand this complex relationship.

Limitations

While the statistical analysis did not yield significant results, it emphasizes the need for further research. In pediatric epilepsy, this may involve studying a broader range of ASMs and dosages, as well as larger and more diverse patient samples. Targeted investigations into specific subgroups, such as those defined by age, gender, or treatment duration, could help to uncover more relevant and generalizable associations.

Conclusion

In conclusion, the limited sample size, especially for the LEV group, calls for cautious interpretation of these results. Future studies should focus on larger cohorts and consider other variables, such as treatment duration, dose escalation, and patient-specific characteristics, to better understand the relationship between ASM dosages and thyroid function. Moreover, while VPA and LEV are commonly prescribed for pediatric epilepsy, their influence on thyroid function appears limited based on the data from this cohort. Further research involving larger patient samples and long-term follow-up is essential to confirm these findings and guide therapeutic approaches, especially in children with pre-existing thyroid conditions or those at risk of developing thyroid dysfunction.

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Ethic Committee: The study was conducted in accordance with Declaration of Helsinki. Written informed consent for publication of identifying images or other personal or clinical details was obtained from both of the parents of the patient.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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