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Thyroid Dysfunction in Children Receiving Antiepileptic Drug Therapy: A Retrospective Cohort Study

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Abstract

Background

Antiepileptic drugs (AEDs) are widely used in pediatric epilepsy. Long-term AED therapy has been associated with alterations of thyroid hormone metabolism and thyroid function, but data on the prevalence and clinical significance of AED-associated thyroid dysfunction in children are limited and inconsistent.

Objective

The primary objective of this study was to determine the frequency and characteristics of documented thyroid dysfunction among children receiving antiepileptic drug (AED) therapy. Secondary objectives were to compare the frequency and types of thyroid abnormalities across older-generation, newer-generation, and combined AED exposure groups, as well as between children receiving monotherapy and polytherapy.

Methods

In this retrospective cohort study, 547 children with epilepsy treated with AEDs at Latifa Hospital and Al Jalila Children's Specialty Hospital, Dubai (UAE), between January 2018 and December 2023 were retrospectively reviewed. Demographic data, exposure to AEDs, treatment regimens, and results of thyroid function tests available at the time of the first evaluation were retrieved. Patients were classified according to older- and newer-generation AED exposure and treatment regimen (monotherapy or polytherapy). Thyroid dysfunction was subclinical or overt primary hypothyroidism. Categorical variables were analyzed using the chi-squared test.

Results

Of 547 children (mean age: 10.09 ± 3.96 years), 30 (5.5%) had thyroid dysfunction (24 (80%) subclinical hypothyroidism and six (20%) overt primary hypothyroidism). In affected children, 22 (73.3%) received older-generation AEDs; valproic acid was the most common medication used in this group (15/22; 68.2%). Thyroid dysfunction was found in 17/292 (5.8%) children receiving only older-generation AEDs, 7/176 (4.0%) only newer-generation AEDs, and 6/79 (7.6%) both generations. Levothyroxine treatment was reported in seven (23.3%) affected children; recovery of thyroid function was observed in two (6.7%).

Conclusion

Documented thyroid dysfunction was identified in a minority of children receiving AED therapy, with subclinical hypothyroidism accounting for most cases. No statistically significant association was identified between AED exposure category or treatment regimen and thyroid dysfunction. Given the retrospective design, limited baseline thyroid function assessment, and absence of an untreated control group, causality cannot be established. These findings support an individualized approach to thyroid function assessment and highlight the need for prospective studies to establish evidence-based monitoring recommendations.

Categories: Neurology, Pediatrics, Endocrinology/Diabetes/Metabolism
Keywords: antiepileptic drugs (aeds), childhood epilepsy, epilepsy, hypothyroidism, sub-clinical hypothyroidism, thyroid disorders, thyroid hormone disorders

Introduction

Epilepsy is among the most common chronic medical conditions, affecting approximately 50 million people worldwide [1]. The cumulative annual incidence is 7-8 per 1000 children by age 15 [2], with this age group accounting for approximately 25% of the total number of people with epilepsy.

Anticonvulsant drugs remain the treatment of choice in pediatric epilepsy in the absence of a structural brain defect amenable to epilepsy surgery [3]. Treatment usually needs to be prolonged for at least two to three years. Given the success of antiepileptic monotherapy in approximately 70 percent of patients, they

emphasize how important it is to commence treatment with antiepileptic drugs early and to have a thorough understanding of potential side effects that are associated with their use [4].

Chronic administration of antiepileptic drugs (AEDs) is associated with various metabolic, endocrine, and hormonal complications, as well as different vascular risks and events that can be observed even within the therapeutically recommended antiepileptic medications [5]. In children on AEDs, clinicians closely monitor endocrine disorders, particularly thyroid function.

Thyroid dysfunction may delay growth and development in children and disrupt endocrine homeostasis in adults because thyroid hormones are vital to the development and regulation of the metabolic state of many tissues. Especially during the first three years, these hormones are essential for brain development and also mediate, beyond brain development, different metabolic pathways, bone maturation, and growth.

Therefore, any apparent thyroid abnormality may result in delayed growth and intellectual disability [3]. Moreover, subclinical thyroid disorders have been associated with proatherogenic and serum lipid disorders in children and increased risk of cardiovascular disease in adults. However, the association of this habit in children remains poorly understood [3].

In 1961, Oppenheimer et al. demonstrated that phenytoin (diphenylhydantoin) significantly reduced serum protein-bound iodine levels in patients with epilepsy without causing clinically apparent hypothyroidism. These findings suggested that phenytoin influences thyroid hormone measurements through alterations in thyroid hormone-protein binding rather than direct thyroid dysfunction [6]. However, the reported findings vary according to the type of AED used and the duration of treatment. Furthermore, valproic acid therapy has been associated with an increased risk of subclinical hypothyroidism [7].

Antiepileptic drugs with low protein binding capacity and enzyme-inducing action (e.g., phenobarbital) have a similar effect. Still, they are less pronounced than drugs with high protein binding and enzyme-inducing ability (e.g., phenytoin, carbamazepine). In comparison to more recent antiepileptic drugs, such as topiramate, gabapentin, lamotrigine, and levetiracetam, there is a lack of knowledge regarding the effects of antiepileptic drugs on thyroid hormones [8]. Several pathways by which AEDs impact thyroid function have been elucidated. These mechanisms include accelerated peripheral conversion of T4 to T3 by antiepileptic drugs, increased T4 metabolism via hepatic P450 enzyme induction, and competition for binding to T4-binding globulin by antiepileptic drugs and thyroid hormones [9]. Previous studies have demonstrated that antiepileptic drugs (AEDs) can affect thyroid function, resulting in alterations in thyroid hormone concentrations and thyroid-stimulating hormone (TSH) levels. These changes may occur following treatment initiation and vary depending on the AED used and the duration of therapy [6, 10].

Materials And Methods

Study design and settings

This is a retrospective cohort study that took place at two pediatric neurology centers in Dubai, United Arab Emirates (Latifa Hospital and Al Jalila Children's Specialty Hospital). The medical records of all children who visited the neurology clinics between January 2018 and December 2023 were retrospectively analyzed to identify thyroid dysfunction in children treated with antiepileptic drugs (AEDs).

A total of 2279 medical records from pediatric neurology clinics were screened for eligibility. Of these, 547 patients were included in the final analysis based on the predefined inclusion and exclusion criteria. As this was a retrospective analysis of available medical records, no prospective sample size calculation was performed. The sample size was determined by the number of eligible patients identified during the study period.

Inclusion/exclusion criteria

All children included in the study were diagnosed with epilepsy, treated with either monotherapy or polytherapy, and had available clinical records documenting that thyroid function was assessed while receiving AED therapy.

The study excluded patients who developed thyroid disorders prior to starting AED therapy; patients with chronic systemic illnesses related to hypothalamic-pituitary-thyroid (HPT) axis dysfunction; patients with structural brain disorders that might impact the HPT axis; and patients taking drugs that can alter the metabolism of thyroid hormones. In addition, patients who did not take their AEDs regularly or whose medical charts were incomplete were excluded from the study.

Patients with documented thyroid disorders preceding AED initiation were excluded. However, documented normal thyroid function before AED initiation was not a mandatory inclusion criterion, as thyroid function tests at baseline were not consistently available in the retrospective records. Consequently, even with no documented thyroid diagnosis before AED initiation, previously undiagnosed thyroid dysfunction could still be present. This limitation was considered when interpreting thyroid abnormalities identified during AED

treatment.

Patients were classified according to the generation of antiepileptic drugs (AEDs) received. Group 1 comprised patients treated with older-generation AEDs, including phenobarbital, phenytoin, carbamazepine, and valproic acid. Group 2 comprised patients treated with newer-generation AEDs, including lamotrigine, levetiracetam, topiramate, and vigabatrin. For comparative analysis, treatment exposure was further categorized into three mutually exclusive categories: older-generation AEDs only, newer-generation AEDs only, and a combination of older- and newer-generation AEDs.

Additionally, patients were classified according to treatment regimen. Monotherapy was defined as treatment with a single AED, whereas polytherapy was defined as the concurrent use of two or more AEDs.

Data collection

Data were collected retrospectively from the electronic health records of both hospitals, including patient age, patient gender, epilepsy diagnosis, results of brain imaging, age when antiepileptic drug (AED) treatment was initiated, AED generation category, monotherapy vs. polytherapy, length of treatment, and all relevant data pertaining to the evaluation of thyroid function.

Data were retrospectively collected from electronic medical records using a standardized data collection form. The recorded variables included age, sex, epilepsy-related clinical characteristics, brain imaging findings, age at AED initiation, treatment regimen (monotherapy or polytherapy), AED generation category, and available information regarding thyroid function assessment.

The data collection form also recorded whether thyroid function screening was documented before AED initiation or during treatment, thyroid testing frequency where available, documented thyroid abnormalities, levothyroxine treatment, duration-related information, and reported normalization of thyroid function following AED treatment modification or withdrawal.

Because this was a retrospective study, the availability and completeness of these variables depended on the original clinical documentation.

Thyroid function assessment

Thyroid function assessment was evaluated retrospectively based on the available clinical documentation. Pretreatment thyroid function screening was recorded in 20 of the 547 patients (3.7%), while the data collection form indicated thyroid function screening during AED therapy in 199 patients (36.4%).

Thyroid function assessment was not conducted under a standardized prospective protocol. Consequently, the availability, indications, and frequency of testing may have differed between patients. In addition, baseline thyroid function results were unavailable for most participants, limiting the ability to distinguish pre-existing thyroid abnormalities from those first identified during AED treatment.

Documented thyroid abnormalities were categorized as subclinical hypothyroidism or overt primary hypothyroidism according to the biochemical definitions described below.

Definition of thyroid dysfunction

Subclinical hypothyroidism was defined as an elevated serum thyroid-stimulating hormone (TSH) concentration with a free thyroxine (FT4) concentration within the laboratory reference range. Overt primary hypothyroidism was defined as elevated TSH accompanied by reduced FT4.

These classifications were based on thyroid function abnormalities documented in the clinical records. Because pretreatment testing was not consistently available, abnormalities first documented during AED therapy were not necessarily considered newly developed or causally attributable to treatment.

Statistical analysis

Statistical analyses were performed using SPSS Statistics, version 29 (IBM Inc., Armonk, NY, USA). Continuous variables were summarized using means and standard deviations where appropriate, while categorical variables were presented as frequencies and percentages.

Comparisons of documented thyroid dysfunction across mutually exclusive AED exposure categories (older-generation only, newer-generation only, and combined exposure) and between monotherapy and polytherapy groups were performed using Pearson's chi-squared test. A p-value of less than 0.05 was considered statistically significant.

The analyses were exploratory and unadjusted for potential confounding variables. Accordingly, observed

associations were not interpreted as evidence of causality.

Ethical approval

The research was evaluated and approved by the Institutional Review Board of Dubai Health (IRB-267) on September 18, 2024. All participants' identities were kept confidential during the entire duration of the research. To safeguard the identity of each participant, all information about them was removed prior to the examination of the collected data.

Results

Study population and demographic characteristics

A total of 2279 medical records of children attending the neurology clinics between January 2018 and December 2023 were reviewed, of which 547 (24.0%) patients fulfilled the study eligibility criteria and were included in the final analysis. Figure *1* illustrates the patient selection process and classification according to antiepileptic drug (AED) exposure.

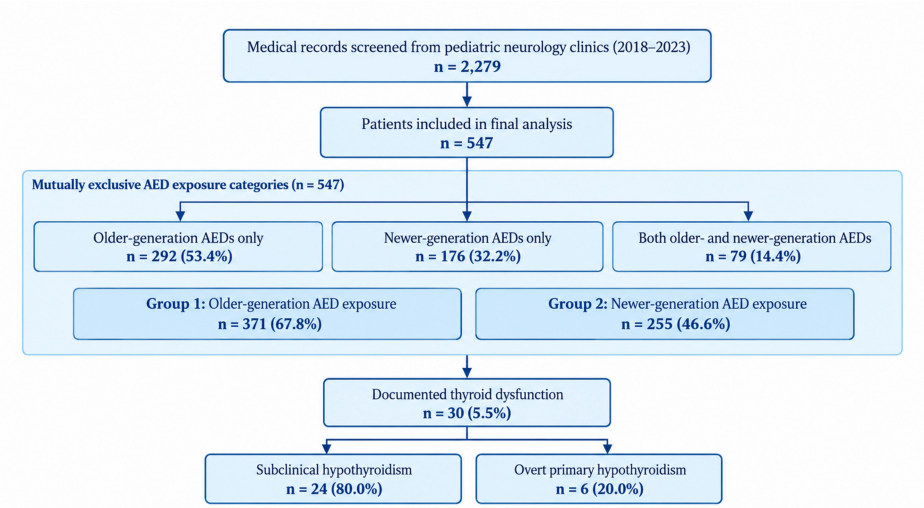


FIGURE 1: Patient selection, antiepileptic drug exposure groups, and thyroid dysfunction classification

Flowchart showing patient selection, AED exposure groups, and thyroid dysfunction classification among 547 children.

AED - antiepileptic drug

The mean age of the study population was 10.09 ± 3.96 years (range: 1-17 years). Of the 547 children, 302 (55.2%) were male, and 245 (44.8%) were female. Documented thyroid dysfunction was identified in 30 (5.5%) patients. The distribution of affected patients by AED exposure category is shown in Figure *2*.

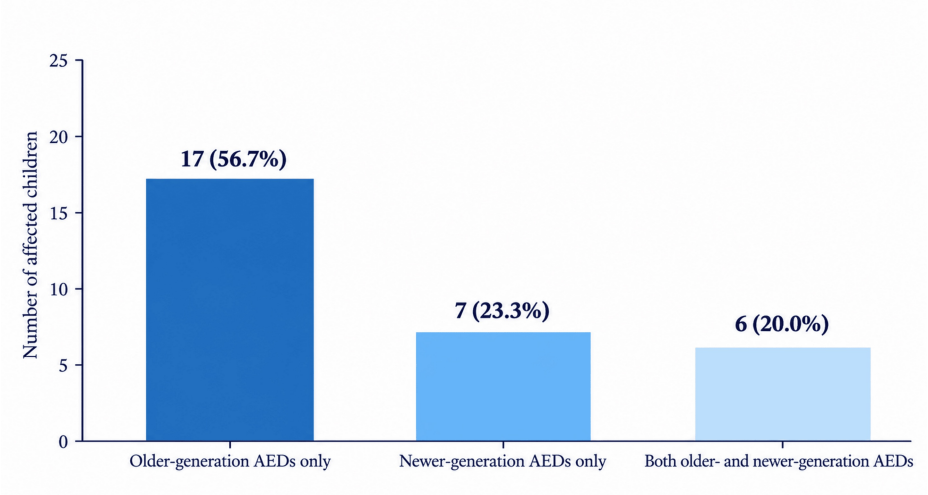


FIGURE 2: Thyroid dysfunction by AED exposure category

Distribution of 30 affected children according to older-generation, newer-generation, or combined AED exposure.

AED - antiepileptic drug

Characteristics of thyroid dysfunction

Among the 30 children with documented thyroid dysfunction, 24 (80.0%) demonstrated subclinical hypothyroidism, characterized by elevated thyroid-stimulating hormone (TSH) levels with normal free thyroxine (FT4) levels. The remaining six (20.0%) had overt primary hypothyroidism, defined as elevated TSH with reduced FT4 levels. The distribution of thyroid dysfunction types is illustrated in Figure *3*.

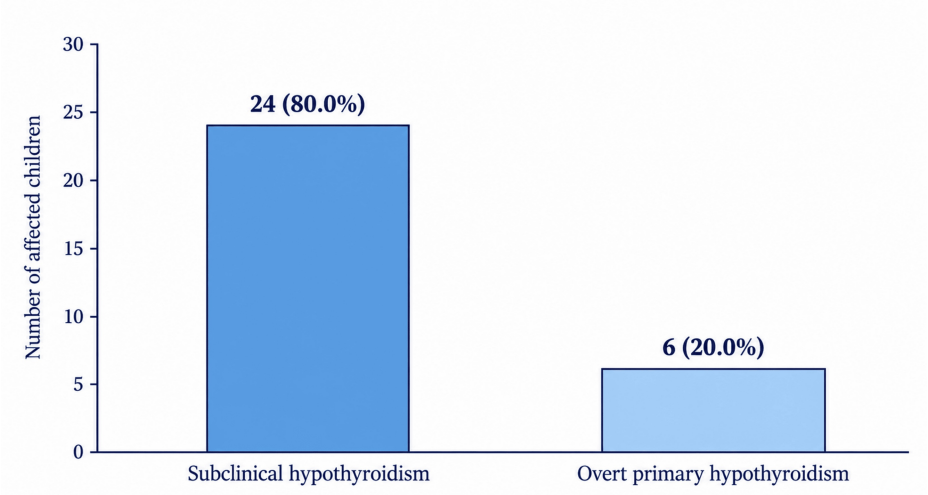


FIGURE 3: Types of thyroid dysfunction

Distribution of subclinical hypothyroidism (n = 24, 80.0%) and overt primary hypothyroidism (n = 6, 20.0%).

Treatment regimens and thyroid function screening

Regarding AED treatment regimens, 417 (76.2%) children received monotherapy, whereas 130 (23.8%) received polytherapy, defined as treatment with two or more AEDs.

Thyroid function testing before the initiation of AED therapy was documented in 20 (3.7%) patients, while thyroid function testing during treatment as part of routine surveillance was recorded in 199 (36.4%) patients.

Regarding AED exposure, 371 (67.8%) children received older-generation AEDs, including phenobarbital, phenytoin, carbamazepine, and valproic acid. A total of 255 (46.6%) patients received newer-generation AEDs, including lamotrigine, levetiracetam, topiramate, and vigabatrin. These categories were not mutually exclusive because some children received medications from both generations.

Timing of thyroid dysfunction

Among the 30 children with documented thyroid dysfunction, the first recorded thyroid abnormality occurred within five years of AED initiation in 16 patients (53.3%), including four patients (13.3%) within the first year.

However, because pretreatment thyroid function was not documented for most patients and subsequent testing was not performed at standardized intervals, these findings represent the timing of first documented detection rather than confirmed onset of thyroid dysfunction. Accordingly, a causal temporal relationship between AED initiation and thyroid dysfunction could not be established.

Thyroid dysfunction according to individual AED exposure

Among the 30 patients with thyroid dysfunction, 22 (73.3%) had received older-generation AEDs. Valproic acid was the most frequently reported older-generation medication among affected patients, used in 15 (68.2%) of the 22 children, followed by carbamazepine in nine (40.9%) and phenobarbital in one (4.5%). The distribution of thyroid dysfunction according to individual older-generation AEDs is illustrated in Figure *4*.

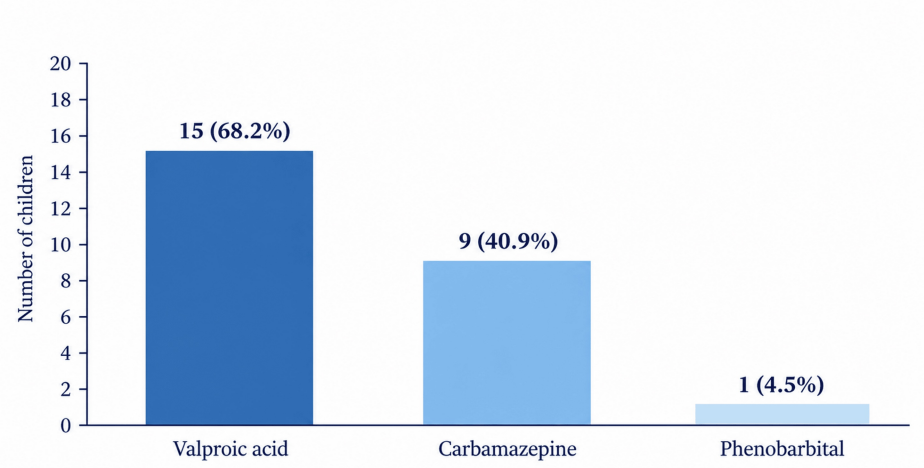


FIGURE 4: Thyroid dysfunction by older-generation AEDs

Distribution of individual older-generation AED exposure among 22 affected children. Medication categories may overlap.

AED - antiepileptic drug

Newer-generation AED exposure was documented in 13 (43.3%) of the 30 children with thyroid dysfunction. Among these 13 patients, lamotrigine and levetiracetam were each prescribed to six (46.2%) patients, followed by topiramate in two (15.4%) and vigabatrin in one (7.7%). The distribution of thyroid dysfunction according to individual newer-generation AEDs is illustrated in Figure *5*.

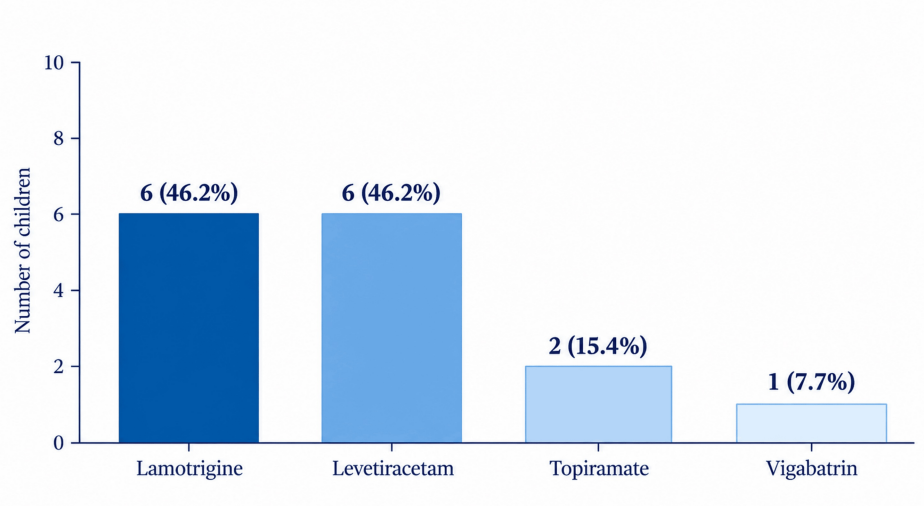


FIGURE 5: Thyroid dysfunction by newer-generation AEDs

Distribution of individual newer-generation AED exposure among 13 affected children. Medication categories may overlap.

AED - antiepileptic drug

Individual medication categories were not mutually exclusive because some patients received multiple AEDs.

Comparison between older- and newer-generation AEDs

For comparative analysis, patients were classified into three mutually exclusive treatment categories. A total of 292 (53.4%) children received older-generation AEDs exclusively, 176 (32.2%) received newer-generation AEDs exclusively, and 79 (14.4%) received a combination of medications from both generations.

Documented thyroid dysfunction was identified in 17 (5.8%) of the 292 children receiving exclusively older-generation AEDs, seven (4.0%) of the 176 receiving exclusively newer-generation AEDs, and six (7.6%) of the 79 receiving a combination of both generations.

Although the proportion of documented thyroid dysfunction was numerically higher among patients receiving a combination of older- and newer-generation AEDs, no statistically significant association was identified between AED exposure category and thyroid dysfunction ($\chi^2 = 1.514$, $p = 0.469$).

Among the 17 affected children receiving exclusively older-generation AEDs, 13 (76.5%) had subclinical hypothyroidism, and four (23.5%) had overt primary hypothyroidism. Among the seven affected patients receiving exclusively newer-generation AEDs, all seven (100%) had subclinical hypothyroidism, whereas none (0%) had overt primary hypothyroidism.

Among the six affected patients receiving a combination of older- and newer-generation AEDs, four (66.7%) had subclinical hypothyroidism and two (33.3%) had overt primary hypothyroidism. The association between AED exposure category and type of thyroid dysfunction was not statistically significant in the original analysis ($\chi^2 = 3.008$, $p = 0.222$).

Monotherapy versus polytherapy

Documented thyroid dysfunction was identified in 19 (4.6%) of the 417 children receiving monotherapy and 11 (8.5%) of the 130 children receiving polytherapy.

Although thyroid dysfunction was numerically more frequent among children receiving polytherapy, the difference did not reach conventional statistical significance in the unadjusted Pearson chi-squared analysis ($\chi^2 = 2.916$, $p = 0.088$).

Levothyroxine treatment, dose dependence, and reversibility

Among the 30 patients with documented thyroid dysfunction, seven (23.3%) required levothyroxine treatment.

Thyroid dysfunction was classified as potentially dose-related in 18 (60.0%) patients. Long-term AED exposure was reported in 16 (53.3%) affected children.

Recovery of thyroid function following AED treatment modification or withdrawal was documented in two (6.7%) patients.

Discussion

Principal findings and clinical significance

The present retrospective cohort study sought to investigate abnormalities of thyroid function in 547 children who were receiving antiepileptic drugs (AEDs) at two tertiary pediatric centers in Dubai, United Arab Emirates. Thirty children (5.5%) had thyroid dysfunction. The most common thyroid dysfunction was subclinical hypothyroidism (80%). There were numerically more thyroid abnormalities in children receiving combined older- and newer-generation AEDs and in those receiving polytherapy, but neither association was statistically significant. Previous studies have shown that AED therapy can affect thyroid hormone homeostasis through several pharmacological mechanisms, with the magnitude and pattern of abnormalities depending on the drug used [3,5,9,10].

Our results are consistent with previous pediatric studies showing that subclinical thyroid dysfunction is more commonly observed than overt hypothyroidism in patients on AEDs [3,7,10]. Ilia et al. performed a systematic review and meta-analysis of 945 pediatric patients and found significantly increased odds of thyroid abnormalities in children receiving AEDs compared with controls (odds ratio [OR]: 6.82; 95% confidence interval [CI]: 3.96-11.75) [3]. Elderly patients treated with valproic acid (OR: 9.54; 95% CI: 5.25-17.34) and carbamazepine (OR: 4.08; 95% CI: 1.84-9.04) were more likely to have raised thyroid-stimulating hormone (TSH) concentrations [3]. However, the authors emphasized the uncertain clinical significance of these biochemical abnormalities and the lack of evidence-based recommendations for monitoring [3].

In our cohort, the lower rate of reported thyroid dysfunction compared to some previous studies may be explained by differences in patient characteristics, AED exposure, laboratory definitions, and thyroid function screening practices [3,7,10]. In addition, our findings cannot determine whether the documented thyroid abnormalities developed as a direct result of AED exposure because baseline thyroid function was not always available and the study did not include an untreated comparison group [3,5,9].

Mechanistic heterogeneity across AED classes

The relationship between AED treatment and dysfunction of the thyroid is complicated since many drugs may influence the metabolism of thyroid hormones by different mechanisms, including hepatic enzyme induction, changed protein binding, peripheral hormone metabolism, and hypothalamic-pituitary-thyroid (HPT) axis regulation [5,6,8]. These mechanisms may lead to different biochemical patterns, and therefore it is not appropriate to assume that all AED-induced thyroid abnormalities represent the same underlying endocrine disorder [5,8].

Traditional enzyme-inducing AEDs like carbamazepine, phenobarbital, and phenytoin may increase the hepatic metabolism of thyroid hormones by inducing the drug-metabolizing enzymes responsible for thyroid hormone clearance [5,8]. Increased clearance may decrease circulating concentrations of thyroxine (T4), but the following TSH response may be dependent on the individual's compensatory mechanisms and thyroid reserve [5,8]. Thyroid hormone binding to plasma proteins may also be affected by phenytoin and carbamazepine, leading to changed measured thyroid hormone concentrations without necessarily producing clinically important hypothyroidism [6].

The first report of decreased serum protein-bound iodine concentrations in patients receiving treatment with phenytoin was published by Oppenheimer et al. [6]. This suggested that AEDs may affect thyroid hormone transport and biochemical measurements without overt thyroid dysfunction [6]. Later studies have confirmed the importance of distinguishing between medication-induced changes in circulating thyroid hormone concentrations and true impairment of thyroid gland function [5, 8].
In contrast, valproic acid is not a classical hepatic enzyme-inducing AED, and its effect on thyroid function is believed to be mediated by different mechanisms [5,7]. Proposed pathways include altered regulation of the HPT-axis and thyroid hormone metabolism; however, the exact mechanisms are not fully understood [5,7]. Valproic acid has often been associated with elevation of TSH levels while free thyroxine (FT4) remains within normal limits, leading to a biochemical pattern consistent with subclinical hypothyroidism [3,7,10].

Mikati et al. reported subclinical hypothyroidism in 25.2% of children treated with valproic acid compared with no cases in controls and suggested that younger age, longer duration of treatment, and concomitant use of antiepileptic drugs may be risk factors [7]. These results suggest that the thyroid dysfunction induced by valproate could be related to both drug and patient factors [3,7].
In our cohort, valproic acid was the most frequently reported older-generation medication in children with documented thyroid dysfunction, prescribed to 15 of the 22 affected children exposed to older-generation AEDs (68.2%). However, there was overlap of individual AED exposures, and incidence rates were not

calculated for specific medications. Thus, our results cannot prove that valproic acid increases the risk of thyroid dysfunction as compared with other AEDs.

Traditional versus newer-generation AEDs

While studies suggest that some newer agents may have a less pronounced impact on thyroid hormone concentrations than older enzyme-inducing drugs [3,5,10], the endocrine effects of newer-generation AEDs are still not fully characterized. Levetiracetam, in particular, has been shown to have relatively limited effects on thyroid function in pediatric studies, and thyroid hormone abnormalities have also been reported with other newer-generation medications [3,10].

Yılmaz et al. prospectively studied thyroid function in children on AED monotherapy and observed differences in biochemical thyroid responses according to the medication [10]. Their findings showed that traditional agents and valproic acid could affect thyroid function through different mechanisms, and levetiracetam had no significant thyroid hormone changes during the observation period [10]. However, the current evidence does not suffice to state that all newer-generation AEDs are endocrinologically neutral, not least because long-term pediatric follow-up data are still scarce [3,5].

In our study, thyroid dysfunction was documented in 5.8% of children receiving only older-generation AEDs, 4.0% receiving only newer-generation AEDs, and 7.6% receiving both generations. The combination-exposure group had the highest numerical frequency of thyroid dysfunction but no statistically significant association between AED exposure category and thyroid dysfunction (p=0.469).

Such findings should not be interpreted as evidence of equivalent endocrine safety of older- versus newer-generation AEDs. Medication generation does not fully explain differences in enzyme induction, pharmacokinetic interactions, treatment duration, and underlying patient susceptibility [5,8,9]. Therefore, drug-specific analyses may be more informative when assessing the risk associated with thyroid than general comparisons between traditional and new-generation AED categories [3,5,10].

Confounding subclinical thyroid profiles and seizure subtype susceptibility

Interpretation of thyroid function abnormalities in children receiving AEDs is complicated by several potential confounders, including age, pubertal status, underlying thyroid disease, nutritional status, intercurrent illness, and concurrent medications [5,8,11]. Mild TSH elevation with normal FT4 concentrations does not necessarily reflect persistent thyroid dysfunction and should be interpreted according to clinical features and repeated biochemical assessment [11].

Another challenge is to distinguish AED-related thyroid abnormalities from those linked to the underlying epilepsy syndrome or its clinical management. Different types of seizures in children may require different AED regimens, and those with drug-resistant epilepsy often take multiple medications and undergo more extensive clinical investigations [2,4]. Such differences may introduce confounding by indication, i.e., the association between medication exposure and thyroid dysfunction is partially explained by severity of epilepsy or treatment selection rather than a pharmacological effect [4,5].

Susceptibility of seizure subtypes is an important but poorly studied aspect of AED-associated thyroid dysfunction. Treatment patterns, seizure burden, and associated neurological comorbidities may differ between focal and generalized epilepsy syndromes [2,4]. However, the current evidence does not establish whether specific seizure subtypes independently increase susceptibility to thyroid dysfunction in AED therapy [3,5]. Future studies should include standardized seizure classification, etiology of epilepsy, treatment response, and severity of seizure to clarify these possible relationships [3,4].

We did not conduct detailed analyses by seizure subtype or epilepsy severity in our study. We therefore could not determine if these factors influenced the association between AED exposure and thyroid abnormalities.

Clinical challenges associated with AED polytherapy

Polytherapy is a further clinical challenge as combinations of AEDs may lead to overlapping pharmacokinetic interactions and cumulative endocrine effects [5,8]. Concurrent use of enzyme-inducing and non-enzyme-inducing medications may change drug metabolism, circulating hormone concentrations, and interpretation of thyroid function tests [5,8,12]. Furthermore, polytherapy is often used in children with more severe epilepsy, which can confound the results due to the severity of the disease and the duration of treatment [4,7].

Thyroid dysfunction was seen in 11 of 130 children on polytherapy (8.5%) compared to 19 of 417 children on monotherapy (4.6%) in our cohort. The proportion was numerically higher in children on multiple AEDs, but the difference was not statistically significant by conventional standards (p=0.088).

Previous studies suggested that the co-administration of AEDs might be a risk factor for thyroid abnormalities, especially in children exposed to valproic acid [7]. However, whether this association is due to cumulative drug exposure, pharmacokinetic interactions, longer treatment duration, or characteristics of the underlying epilepsy is unknown [5,7]. Polytherapy may also increase the likelihood of laboratory surveillance and detection of asymptomatic abnormalities, which may contribute to ascertainment bias.
These points emphasize the importance of paying attention to individual drug combinations, duration of treatment, serum drug concentrations, and the severity of epilepsy before concluding that it is the polytherapy that is responsible for thyroid dysfunction [5,8]. Further prospective studies with adequate adjustment for these factors need to be performed to ascertain whether polytherapy per se leads to clinically relevant thyroid dysfunction [3,5].

Central versus peripheral thyroid hormone disconnection

During AED therapy, a clinically important phenomenon is the potential dissociation between circulating levels of thyroid hormone and the expected pituitary response of TSH [5,8]. Some medications have been associated with lower measured FT4 concentrations without a rise in TSH, most notably carbamazepine and phenytoin [8,12]. This pattern may mimic central hypothyroidism in the absence of true hypothalamic or pituitary disease [12, 13]. This biochemical imbalance may be mediated by several mechanisms, including increased peripheral hormone clearance, changes in protein binding, laboratory assay effects, and alteration of thyroid hormone feedback regulation [5,8,12]. Thus, isolated reduction of FT4 with normal TSH does not automatically prove central hypothyroidism in a child on AED therapy [12,13].

The European Thyroid Association recommends the interpretation of suspected central hypothyroidism by both FT4 and TSH measurements, confirming persistent abnormalities and excluding alternative causes before establishing the diagnosis [13]. This distinction is especially important in children receiving drugs that can affect thyroid hormone metabolism or laboratory measurements [8,12,13].

In the present study, thyroid dysfunction was defined by biochemical patterns of subclinical or overt primary hypothyroidism, both of which are characterized by elevated TSH concentrations. Our outcome definition did not capture isolated decreases in FT4 without TSH elevation. This limitation may have led to under-recognition of some AED-induced changes in thyroid hormones and limited our ability to assess the full spectrum of HPT-axis responses.

Long-term neurocognitive and cardiometabolic consequences

Thyroid hormones are vital for growth, skeletal maturation, metabolic regulation, and neurological development in children [11,13]. Overt hypothyroidism has been shown to be detrimental to growth and neurodevelopment, but the long-term consequences of persistent mild subclinical hypothyroidism are unknown [11,14]. The neurocognitive consequences in children with epilepsy are especially challenging to evaluate because epilepsy etiology, seizure burden, neurological comorbidities, and AED-related effects may influence cognitive function [2,4]. These interacting elements make it difficult to determine if mild thyroid dysfunction contributes to learning problems, attention deficit, or impaired cognitive functioning by itself [3,5]. Capalbo et al. conducted a prospective study of children with idiopathic subclinical hypothyroidism and showed that two years of levothyroxine treatment restored TSH concentrations to normal, but did not significantly improve intellectual or neurocognitive outcomes [15]. However, these findings may not be generalized to children receiving AED therapy, because mechanisms underlying thyroid abnormalities might differ [5, 15]. Consideration should also be given to the potential cardiometabolic consequences. Thyroid hormones regulate lipid metabolism, insulin sensitivity, energy expenditure, and cardiovascular physiology [5,14]. Studies looking at indices of thyroid hormone sensitivity have reported associations between changes in thyroid hormone sensitivity and metabolic abnormalities such as diabetes and metabolic syndrome, although these findings do not prove causality or demonstrate similar effects in children on AEDs [14]. In addition, some AEDs can independently influence metabolic parameters, making it more difficult to differentiate between medication-related metabolic effects and those possibly related to thyroid dysfunction [5]. The long-term clinical implications of AED-associated subclinical hypothyroidism are unknown and require study in prospective studies with detailed neurocognitive and cardiometabolic assessment [3,5,15].

Future studies should assess attention, memory, executive function, academic performance and health-related quality of life, as well as longitudinal growth, body mass index, lipid profiles, blood pressure and glucose metabolism [3,14,15]. These studies may help to determine whether persistent biochemical thyroid abnormalities have clinically important consequences or are primarily transient adaptations to medication exposure [3,5].

Therapeutic dilemmas and levothyroxine initiation thresholds

Management of AED-associated subclinical hypothyroidism is a therapeutic dilemma, since mild TSH elevation with normal FT4 concentrations may be transient and does not necessarily require immediate thyroid hormone replacement [3,11]. Therefore, the decision to initiate levothyroxine should take into account the biochemical severity, the persistence of abnormalities, the clinical manifestations, and the possibility of alternative causes [11,12]. Current National Institute for Health and Care Excellence (NICE)

guidance suggests consideration of levothyroxine in children aged two years and older with TSH concentrations of at least 20 mIU/L, or persistent TSH concentrations between 10 and 20 mIU/L on two occasions three months apart [11]. In children with thyroid dysgenesis or clinical features of thyroid dysfunction, treatment may also be considered if TSH levels remain between 5 and 10 mIU/L on two occasions three months apart [11]. These recommendations are applicable to subclinical hypothyroidism in children in general and have not been specifically validated in children with AED-associated thyroid abnormalities [3,11].

The American Thyroid Association has also mentioned the possibility of drugs affecting hepatic metabolism, such as enzyme-inducing AEDs, to affect thyroid hormone clearance and levothyroxine requirements [12]. Therefore, children who are on these medications and have established hypothyroidism may require reassessment of thyroid function and replacement needs when AED therapy is started, changed, or stopped [8,12].

Seven of 30 (23.3%) children with documented thyroid dysfunction in our cohort were treated with levothyroxine. However, retrospective documentation did not provide sufficient longitudinal biochemical data and standardized treatment indications to ascertain whether replacement was initiated according to specific TSH thresholds or clinical criteria.

Only two children (6.7%) regained thyroid function after AED modification or withdrawal. Reversibility of medication-associated biochemical abnormalities has been described, but the limited follow-up information in our study does not allow firm conclusions regarding spontaneous recovery or benefits of modifying AED therapy [5,7,10].

The results of this work underscore the need for individualized management and not treating isolated biochemical abnormalities unnecessarily [3,11]. Seizure control and neurological outcomes should be considered when making decisions regarding AED substitution. Established pediatric endocrine guidance and the overall clinical context should inform decisions regarding levothyroxine [4,11,12].

Evidence-based thyroid screening and monitoring protocols

While there is increasing awareness that AEDs may influence thyroid function, there is no universally accepted AED-specific protocol for thyroid screening in children [3,5]. Available studies vary widely on the selection of AEDs, characteristics of patients, definitions of thyroid dysfunction, intervals of monitoring, or duration of follow-up, limiting the development of standard recommendations [3,7,10].

Only 20 children (3.7%) had documented thyroid testing prior to treatment in our study, and 199 patients (36.4%) had documented routine thyroid surveillance during treatment. Such variation in recorded monitoring reflects the difficulties of retrospective evaluation and may account for the differences in the detection of thyroid abnormalities.

Evidence-based monitoring strategies should distinguish between children with clinical indications for thyroid testing and asymptomatic children without other risk factors [3,11]. NICE suggests that thyroid function testing should be considered in children with abnormal growth, unexplained behavioral changes, or deterioration in school performance and recommends measuring both TSH and FT4 when assessing suspected thyroid dysfunction in children [11].

Individualized baseline assessment can be considered in children on AED therapy in the presence of pre-existing risk factors related to the thyroid, suggestive clinical findings, or anticipated prolonged exposure to medications associated with thyroid hormone alterations [3,5]. Further testing should be symptom-directed, based on growth pattern, drug exposure, and previous biochemical results rather than by a set monitoring interval alone [3,5,11]. After diagnosis of mild subclinical hypothyroidism, repeat assessment is important to confirm persistence and to differentiate transient biochemical changes from clinically significant thyroid dysfunction [11]. Evaluation for alternative causes, including autoimmune thyroid disease when clinically appropriate, may further improve diagnostic accuracy [11].

But the effectiveness and cost-effectiveness of routine thyroid screening in all children on AEDs have not been established [3]. Future prospective studies should determine which patients are most likely to benefit from surveillance, the appropriate frequency of testing, and whether early detection and treatment lead to improvements in clinically meaningful outcomes [3,5].

Future research: thyroid hormone sensitivity indices, genetic susceptibility, and next-generation AEDs

Further studies are needed to identify isolated abnormalities of TSH and FT4 for a more complete understanding of thyroid hormone regulation during AED exposure [5,8]. Future studies should include standardized baseline measurements, serial biochemical evaluations, exposure data specific to medications, seizure characteristics, and long-term clinical outcomes [3,5,10].

Among the promising research directions is the estimation of thyroid hormone sensitivity indices such as thyroid feedback quantile-based index (TFQI), TSH index (TSHI), and thyrotroph T4 resistance index [14]. These indices have been studied as indicators of central thyroid hormone feedback sensitivity and shown to be associated with metabolic outcomes in non-epilepsy populations [14].
However, their diagnostic accuracy, age-specific applicability, and clinical utility in children on AEDs are unvalidated [14]. Future studies should assess the utility of these indices for more accurate identification of clinically relevant thyroid abnormalities compared to traditional TSH and FT4 measurements, controlling for assay variability, pubertal development, and medication effects on thyroid hormone metabolism [5,14].

Another source of interindividual variability in the thyroid responses to AED therapy may be genetic susceptibility. Differences in hepatic drug-metabolizing enzymes, thyroid hormone transport, deiodinase activity, and regulation of the HPT axis may influence biochemical responses to drug exposure [5,8,13]. However, these proposed associations require dedicated pharmacogenomic studies, and no established genetic marker currently supports routine prediction of AED-associated thyroid dysfunction.
Continued investigation into the increasing use of newer-generation AEDs is also warranted. Although some of the newer agents seem to have less clinically relevant hepatic enzyme-inducing interactions, their long-term endocrine effects cannot be assumed to be negligible [3,5,10]. Future studies need to assess individual newer drugs, including brivaracetam, lacosamide, and perampanel, in well-controlled pediatric cohorts using standardized methods of thyroid assessment.

Importantly, future studies should evaluate whether persistent thyroid abnormalities are associated with adverse neurocognitive, growth-related, or cardiometabolic outcomes [3,14,15]. Such evidence would facilitate the development of validated risk-stratification approaches, evidence-based screening protocols, and clinically meaningful thresholds for intervention [3,11].

Strengths and limitations

Strengths of this study include the relatively large pediatric cohort, recruitment from two tertiary pediatric centers, and comparison of thyroid abnormalities by older-generation AED, newer-generation AED, and combined AED exposure categories. Additionally, descriptive information on thyroid function abnormalities in different treatment regimens is also obtained by the presence of monotherapy and polytherapy groups.

However, there are some limitations to be noted. First, the retrospective nature of the study and the limited availability of pretreatment thyroid testing make it difficult to reliably distinguish between pre-existing thyroid dysfunction and abnormalities that are first identified during AED treatment. This is important since the relationship between AED exposure and thyroid function may be subject to drug-specific mechanisms and baseline characteristics of the patient [3,5,8].

Second, thyroid function monitoring was not carried out on a standardized protocol, which could lead to ascertainment bias. Children with more frequent testing may have had a higher chance of asymptomatic biochemical abnormalities being detected, while abnormalities in less frequently tested patients may have gone undetected. Thus, our findings characterize documented thyroid dysfunction rather than the prospectively identified incidence of AED-induced hypothyroidism.

Third, the lack of an untreated control group and the use of unadjusted statistical comparisons limit the causal interpretation. Potential confounding variables such as seizure subtype, severity of epilepsy, duration of treatment, body mass index, pubertal status, thyroid autoimmunity and iodine status were not examined in detail. These factors may influence thyroid function irrespective of drug exposure [3,5,11].

Fourth, AED categories were not mutually exclusive and individual AED-specific incidence rates were not calculated. Therefore, differences in the distribution of individual AEDs in affected children cannot be interpreted as a signal of relatively higher risk for specific medications.

Fifth, our biochemical definition of thyroid dysfunction was limited to primary hypothyroidism. Because AEDs may also reduce FT4 without an increase in TSH, some patterns of drug-related change in thyroid hormone may have been missed [8,12,13].

Finally, limited longitudinal biochemical follow-up precluded detailed assessment of dose dependence, persistence, reversibility, levothyroxine requirements, and long-term clinical consequences. These limitations are in line with the more general methodological difficulties highlighted in the literature and emphasize the need for standardized prospective pediatric studies [3,5,10].

Clinical recommendations

Clinicians should be aware that AEDs can affect thyroid hormone homeostasis through heterogeneous mechanisms, and biochemical abnormalities should be interpreted in the light of an individual medication, clinical presentation, and underlying patient characteristics [3,5,8]. Elevated TSH with normal FT4 concentrations should not lead to levothyroxine treatment without confirmation and consideration of other

causes [11].

Individualized thyroid assessment may be indicated in children presenting with clinical signs, abnormal growth patterns, other risk factors for thyroid disease, or prolonged exposure to medications known to alter thyroid hormone levels [3,5,11]. Careful interpretation of discordant FT4 and TSH results may also be required in children receiving enzyme-inducing AEDs, particularly when central hypothyroidism is being considered [8,12,13].

The decision to start levothyroxine therapy should be, according to current guidelines for pediatric hypothyroidism, based on biochemical severity, persistence, and clinical findings [11,12]. Universal recommendations for AED-specific monitoring intervals or treatment thresholds are not yet possible and require prospective studies [3,5].

Conclusions

Thyroid dysfunction was documented in 5.5% of children on AED therapy in this retrospective two-center cohort, with subclinical hypothyroidism being the most common biochemical abnormality. Children who received combined old- and newer-generation AEDs and those on polytherapy showed a greater number of thyroid abnormalities, but these associations were not statistically significant. Mechanisms of AED-associated thyroid alterations are heterogeneous and may include hepatic enzyme induction, altered thyroid hormone metabolism, changes in protein binding, and disturbances of feedback regulation of the HPT axis.

The absence of systematic baseline testing and standardized monitoring, and the absence of an untreated control group, limit causal interpretation and preclude definitive conclusions regarding risk specific to medication. Clinicians should be aware of the possibility of transient biochemical abnormalities and discordant thyroid hormone profiles when interpreting thyroid function tests in children on AEDs. Until prospective studies establish standardized screening protocols, levothyroxine initiation thresholds, and the long-term neurocognitive and cardiometabolic implications of these abnormalities, individualized monitoring and evidence-based treatment decisions are appropriate.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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