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*Original article*

# Effect of Valproate and Levetiracetam Monotherapy on Thyroid Function in Children with Epilepsy: A Retrospective Comparative Study at Tripoli University Hospital, Libya

**Asma Hussien**

*Department of Pediatric Neurology, Tripoli University Hospital, Faculty of Medicine, Tripoli University, Libya.*
***Email.*** *asmahussien2@gmail.com*

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*Epilepsy; Children; Valproate; Levetiracetam; Thyroid Function; TSH; Free Thyroxine; Antiseizure Medications.*

**Abstract**

Antiseizure medications (ASMs) are essential for the management of childhood epilepsy, but some may be associated with alterations in thyroid function. Valproate and levetiracetam are commonly used in children with epilepsy, and their effects on thyroid function may differ. Aim: To evaluate and compare thyroid function test abnormalities among children with epilepsy receiving valproate (Depakin) or levetiracetam (Keppra) monotherapy. This retrospective comparative study included 120 children aged 1–14 years with epilepsy diagnosed more than one year before assessment. It was conducted at the outpatient clinics of Tripoli University Hospital, Libya, using medical records from January 2024 to January 2026. Participants were divided into two groups: 60 children receiving valproate monotherapy and 60 receiving levetiracetam monotherapy. Children with documented hypothyroidism before starting ASM were excluded. Thyroid function patterns were categorized according to recorded thyroid-stimulating hormone (TSH) and free thyroxine (FT4) results. In the valproate group, 41 children (68.3%) had normal thyroid function tests, whereas 19 children (31.7%) had abnormal patterns: 10 children (16.7%) had elevated TSH with low FT4, and 9 children (15.0%) had elevated TSH with normal FT4. In the levetiracetam group, 50 children (83.3%) had normal thyroid function tests and 10 children (16.7%) had abnormal results: 4 children (6.7%) had elevated TSH with low FT4, and 6 children (10.0%) had elevated TSH with normal FT4. The prevalence of abnormal thyroid function patterns was 15.0 percentage points higher in the valproate group (31.7% vs. 16.7%; Chi-square = 3.67, p = 0.055; OR 2.32, 95% CI 0.98–5.47). In this study population, abnormal thyroid function patterns were more frequent among children receiving valproate monotherapy than among those receiving levetiracetam monotherapy. These findings support further investigation of thyroid function in children treated with ASMs. Prospective studies with standardized laboratory measurements and adjustment for potential confounding factors are needed.

## Introduction

Epilepsy is one of the most common chronic neurological disorders in childhood and often requires long-term treatment with ASMs. Effective treatment aims to achieve seizure control while minimizing adverse effects that may influence children's growth, development, and overall health [1]. Thyroid hormones play an essential role in brain development, growth, metabolism, and neurological function. Thyroid dysfunction during childhood may have important clinical consequences, particularly in children with pre-existing neurological disorders. Understanding the possible relationship between ASM use and thyroid function is therefore clinically relevant [2, 3].

Valproate is a widely used ASM in pediatric practice. Although effective for several seizure types, studies have reported associations between valproate treatment and alterations in thyroid hormone measurements, including changes in TSH and FT4 [4-10]. Subclinical hypothyroidism has been described in roughly one quarter to one third of children treated with valproate in some series [7, 11], and TSH elevation has been related to serum valproate level, dose, or treatment duration [6, 12]. The underlying mechanisms are not completely established [3, 10].

Levetiracetam is another commonly prescribed ASM. It has a different pharmacological mechanism and generally fewer recognized metabolic interactions than several older ASMs [10, 13, 14]. Nevertheless, its potential association with thyroid function abnormalities remains a relevant clinical question [15-18]. Previous studies investigating thyroid function in children receiving ASMs have reported variable findings [6, 7, 13, 19-23]. Systematic reviews and meta-analyses have also addressed this question [24-26]. Differences in study populations, medication exposure, treatment duration, laboratory reference ranges, and underlying clinical characteristics may contribute to these inconsistencies.

The present study compares thyroid function test patterns in children with epilepsy receiving valproate or levetiracetam monotherapy at Tripoli University Hospital, Libya. The findings may contribute to the limited local evidence regarding thyroid function in children receiving long-term ASM treatment.

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## Methods

### *Study design and settings*

This was a retrospective comparative observational study based on the review of medical records of children with epilepsy receiving ASM monotherapy and attending the outpatient clinics of Tripoli University Hospital, Tripoli, Libya from January 2024 to January 2026, within the context of pediatric neurology services

### *Study population*

The study included 120 children with epilepsy, comprising 75 females (62.5%) and 45 males (37.5%). Participants were divided into two equal groups according to their ASM: Group 1, 60 children receiving valproate (Depakin) monotherapy; Group 2, 60 children receiving levetiracetam (Keppra) monotherapy. All included children had an epilepsy diagnosis dating back more than one year.

### *Inclusion and Exclusion Criteria*

The study included children aged 1–14 years with a documented diagnosis of epilepsy for more than one year who had received monotherapy with either valproate or levetiracetam during the relevant study period. Eligible participants were required to have available thyroid function test results documented in their medical records and no documented history of hypothyroidism prior to the initiation of antiseizure medication (ASM).

Patients were excluded if they had documented hypothyroidism before starting ASM therapy or a pre-existing thyroid disorder. Children who received concomitant treatment with other antiseizure medications during the relevant assessment period were also excluded. Additionally, patients with incomplete medical records or missing essential thyroid function test results were excluded from the analysis.

### *Data collection*

Data were collected retrospectively from the medical records. Variables included sex, ASM used, and thyroid function test results. The principal laboratory variables were TSH and FT4. FT3 measurements, medication dose, and duration of medication exposure were recorded and analyzed where available.

### *Assessment of thyroid function*

Thyroid function patterns were categorized according to recorded TSH and FT4 results. Laboratory results were interpreted using the reference ranges appropriate to the child's age and the performing laboratory.

### *Statistical analysis*

Continuous variables were summarized as means and standard deviations or medians and interquartile ranges. Categorical variables were reported as frequencies and percentages. Proportions of children with normal and abnormal thyroid function tests were compared using the chi-square test or Fisher's exact test.

## Results

A total of 120 children with epilepsy were included: 75 (62.5%) were female and 45 (37.5%) were male. Sixty children received valproate monotherapy and 60 received levetiracetam monotherapy.

**Table 1. Characteristics of the study population (n = 120)**

| Variable / Characteristic | Valproate (n = 60) | Levetiracetam (n = 60) | Total (n = 120) | p-value |
|---|---|---|---|---|
| Female, n (%) | 40 (66.7%) | 35 (58.3%) | 75 (62.5%) | 0.345 |
| Male, n (%) | 20 (33.3%) | 25 (41.7%) | 45 (37.5%) | 0.345 |
| Medication dose, mg/kg/day | 20–40 mg/kg/day | 20–40 mg/kg/day | 20–40 mg/kg/day | - |
| Duration of ASM exposure, months | 36–60 months | 30–48 months | 30–60 months | - |

Among the 60 children receiving valproate, 41 children (68.3%) had normal thyroid function tests, whereas 19 children (31.7%) demonstrated abnormal patterns: 10 children (16.7%) had elevated TSH with low FT4, and 9 children (15.0%) had elevated TSH with normal FT4.

Among the 60 children receiving levetiracetam, 50 children (83.3%) had normal thyroid function tests, whereas 10 children (16.7%) had abnormal patterns: 4 children (6.7%) had elevated TSH with low FT4, and 6 children (10.0%) had elevated TSH with normal FT4.

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**Table 2. Distribution of thyroid function patterns by treatment group (n = 120)**

| Thyroid Function Pattern | Valproate (n = 60) | Levetiracetam (n = 60) | Total (n = 120) | p-value |
|---|---|---|---|---|
| Normal Thyroid Function | 41 (68.3%) | 50 (83.3%) | 91 (75.8%) | 0.055 |
| Any Abnormal Pattern | 19 (31.7%) | 10 (16.7%) | 29 (24.2%) | 0.055 |
| Elevated TSH with Normal FT4 | 9 (15.0%) | 6 (10.0%) | 15 (12.5%) | 0.409 |
| Elevated TSH with Low FT4 | 10 (16.7%) | 4 (6.7%) | 14 (11.7%) | 0.088 |

**Table 3. Effect estimates for abnormal thyroid function patterns (Valproate vs. Levetiracetam)**

| Measure / Outcome | Estimate (95% CI) |
|---|---|
| Absolute Risk Difference | +15.0 percentage points (95% CI: -0.3% to +30.3%) |
| Risk Ratio (RR) | 1.90 (95% CI: 0.97 to 3.72) |
| Unadjusted Odds Ratio (OR) | 2.32 (95% CI: 0.98 to 5.47) |
| Elevated TSH with Low FT4 (VPA vs. LEV) | 16.7% vs. 6.7%, OR = 2.80 (95% CI: 0.81–9.65) |
| Elevated TSH with Normal FT4 (VPA vs. LEV) | 15.0% vs. 10.0%, OR = 1.59 (95% CI: 0.52–4.86) |

Figure 1 illustrates the distribution of thyroid function test patterns in the valproate (n = 60) and levetiracetam (n = 60) monotherapy groups. Normal thyroid function was recorded in 68.3% of the valproate group and 83.3% of the levetiracetam group, whereas abnormal patterns were observed in 31.7% and 16.7%, respectively. Elevated TSH with low FT4 was more frequent in the valproate group (16.7% vs. 6.7%), as was elevated TSH with normal FT4 (15.0% vs. 10.0%).

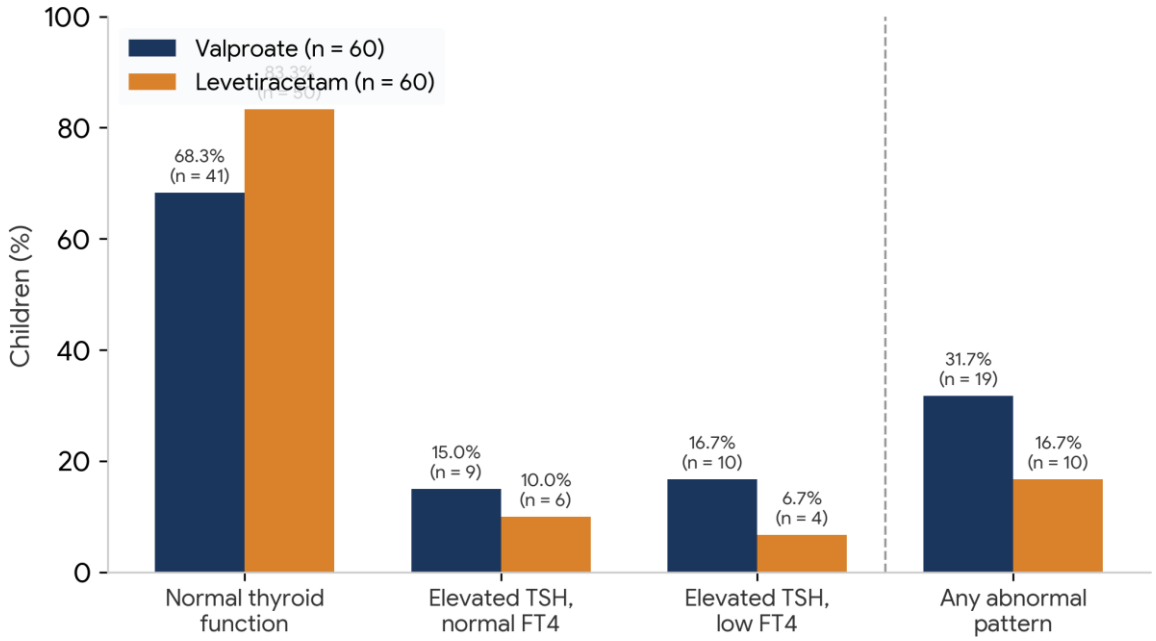



***Figure 1. Distribution of thyroid function patterns (normal, elevated TSH with normal FT4, elevated TSH with low FT4, and any abnormal pattern) in children with epilepsy receiving valproate or levetiracetam monotherapy. Values are percentages of each group (n = 60 per group), with the number of children in parentheses.***

The corresponding effect estimates are shown in Figure 2. Odds ratios were above 1 for all abnormal patterns, favoring a higher occurrence with valproate; however, all 95% confidence intervals included or bordered 1 (any abnormal pattern: OR 2.32, 95% CI 0.98–5.47; p = 0.055).

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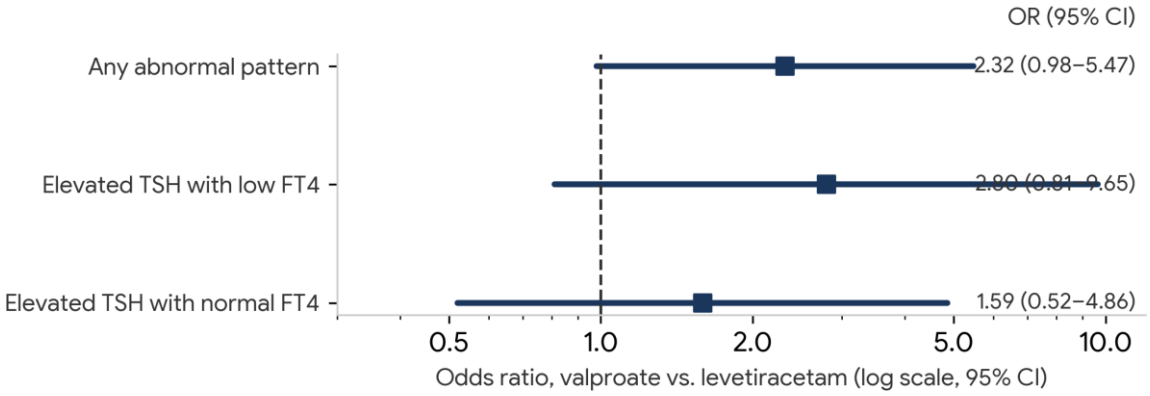



***Figure 2. Forest plot of unadjusted odds ratios (valproate vs. levetiracetam) for abnormal thyroid function patterns. Squares indicate point estimates and horizontal lines indicate the 95% confidence intervals; the dashed line marks no difference (OR = 1).***

## Discussion

In this retrospective comparison of 120 children with epilepsy, abnormal thyroid function patterns were more frequent in children treated with valproate monotherapy (31.7%) than in those treated with levetiracetam monotherapy (16.7%). This finding is consistent with literature reporting alterations in thyroid hormone measurements in children treated with valproate [4, 6, 7, 9, 22, 26, 27]. Reported frequencies of subclinical hypothyroidism during valproate treatment are around 25-30% in some series [7, 11]; the abnormal rate in our valproate group also includes children with low FT4. However, the difference between the groups did not reach conventional statistical significance (p = 0.055), and its confidence interval included 1, so it should be interpreted as a trend rather than a confirmed association.

Isolated elevation of TSH with normal FT4 corresponds biochemically to subclinical hypothyroidism but may be transient or evolve [6, 10, 18, 28]. Normalization of TSH after valproate withdrawal has been reported [6]. Proposed mechanisms include effects on peripheral conversion of thyroid hormones, hormone-binding proteins, and thyroid gland function [3, 10]. The proportion of abnormal results in the levetiracetam group (16.7%) indicates that thyroid abnormalities in children with epilepsy are not limited to one drug and may also relate to the underlying disease, concomitant factors, or laboratory variability [10, 14, 15]. Other comparative studies found no significant effect of levetiracetam on thyroid function tests, including no subclinical hypothyroidism at 12 months in one cohort [7, 10, 27]; the higher rate in our sample may reflect the limits of retrospective record review, such as non-standardized timing of testing and differences in reference ranges.

Serum level, dose, and duration of valproate therapy have been related to TSH elevation [6, 12]; these variables could not be adjusted for in the present study, which limits comparison between groups. The clinical implication is that periodic monitoring of thyroid function (TSH and FT4) is reasonable in children on long-term valproate [6, 8-10, 29].

## Conclusion

Abnormal thyroid function patterns were more frequent among children receiving valproate monotherapy than among those receiving levetiracetam monotherapy. These findings support further investigation of thyroid function in children treated with ASMs.

## Recommendations

Routine thyroid function assessment, including serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4), is recommended before initiating long-term antiseizure monotherapy. Periodic clinical and biochemical monitoring should subsequently be performed every 6–12 months, particularly in children receiving valproate therapy, to facilitate the early detection of potential thyroid dysfunction. When abnormal TSH or FT4 levels are identified, repeat laboratory testing after 4–8 weeks is recommended to distinguish transient or subclinical alterations from persistent thyroid dysfunction before establishing a diagnosis or making treatment-related decisions.

Antiseizure medications should not be abruptly modified or discontinued solely on the basis of borderline or asymptomatic thyroid function abnormalities. Decisions regarding treatment adjustments should be made following careful clinical assessment and consultation with a pediatric neurologist, taking into consideration both seizure control and thyroid function status.

### *Conflict of Interest*

The authors declared no conflict of interest.

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