Original Article

Alteration of Thyroid Hormone Levels in Children with Epilepsy, Treated with Sodium Valproate Monotherapy

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Abstract

Background*: Epilepsy represents the most frequent neurological condition in the pediatric population, frequently necessitating extended, and occasionally permanent, medical management. Valproicacid (VPA), also known as sodium valproate, is a widely used, broad-spectrum antiepileptic medication for children.*

Objective*: This investigation aimed to assess alterations in thyroid hormone concentrations in epileptic children following six months of VPA treatment.*

Methods*: A prospective observational study was conducted in the pediatrics department, utilizing both outpatient and inpatient services at Mymensingh Medical College Hospital, Mymensingh. Following comprehensive history-taking and clinical assessment, 80 children with epilepsy, treated exclusively with VPA, were enrolled. Thyroid function tests were performed before initiating VPA and again six months later. Serum levels of FT_3, FT_4, and TSH were measured on the same day using radioimmunoassay kits. Sociodemographic data were collected and analyzed using SPSS software, version 23.0.*

Results*: Among the 80 participants, 49(61.3%) were male and 31(38.8%) female. The average age was 4.81 years (SD±2.06), with 65 children aged between 2 and 5 years. Baseline thyroid function (TSH, FT_3, FT_4) was normal in all (100%) subjects. At the six-month follow-up, 19 out of 80 children (23.8%) exhibited subclinical hypothyroidism (TSH >6.63IU/ml), a statistically significant finding ($p<0.001$). Only 7.5% of children had FT_3 levels below the normal range (<2.8 pg/ml) after six months of therapy.*

Conclusion*: Therefore, this study concludes that treatment with VPA carries a risk of inducing subclinical hypothyroidism.*

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Keywords: *Epilepsy, Valproic Acid, Subclinical Hypothyroidism,Antiepileptic drug, Growth retardation*

Introduction

Epilepsy is diagnosed following at least two unprovoked seizures occurring more than 24 hours apart, a single unprovoked seizure with a high likelihood of recurrence within a decade, or confirmation of a specific epilepsy syndrome[1]. While controllable withmedication based on seizure type and severity, it is generally not curable[2]. This disorder is particularly prevalent in populations with increased prenatal risks, higher rates of central nervous system infections, and other childhood neurological conditions. The global lifetime prevalence is approximately 7.60 per 1000 people, with estimates of 9.2 and 7.7 per 1000 in low-and middle-income countries, respectively. Prevalence in children under 18 is 8.2 per 1000, similar to the adult rate of 8.5 per 1000[3]. A large majority (96.0%) in one survival study believed epilepsy is a medical condition treatable with antiepileptic drugs[4]. The mainstay of management is antiepileptic drug (AED) therapy, often required long-term or for life[5]. Valproate is extensively prescribed for both partial and generalized epilepsy in children and adolescents[6,7]. As the sodium salt of valproic acid, this branched-

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chain carboxylic acid anticonvulsant is also used for bipolar disorder, migraines, and anxiety disorders. It is primarily administered orally, has excellent oral bioavailability, is highly protein-bound (>90.0%), undergoes complete hepatic metabolism via glucuronidation and oxidation, and is renaly excreted. The potential interaction between AEDs and thyroid hormone levels is a significant clinical concern, as even slight disruptions in thyroid metabolism during childhood can impair growth, development, cognition, and neuromuscular function[8]. The influence of both epilepsy and its treatment on thyroid function has garnered increasing interest. Most pediatric studies on drugs like carbamazepine, oxcarbazepine, and phenobarbital report reduced thyroxine and free triiodothyronine levels with normal or elevated TSH[9,10,11,12,13]. The relationship between valproic acid (VPA) and thyroid dysfunction, however, remains inconsistent. Some research indicates VPA can induce subclinical hypothyroidism, characterized by elevated TSH (5-25 mIU/mL or higher) with stable or decreased FT3 levels[14,15,16,17,18]. while otherstudies show no significant hormonal changes[19,20,21]. Debated risk factors for VPA-induced thyroid issues include patient age, treatment duration, dosage, and drug serum levels. This study was designed to examine the short-term impact of VPA monotherapy on thyroid function in children with newly diagnosed epilepsy.

Methods

This prospective observational research was carried out in the pediatrics unit of Mymensingh Medical College Hospital, Mymensingh, from July 2018 to January 2020. Participants included children aged 2–12 years with a new diagnosis of epilepsy and prescribed valproic acid (VPA) as sole therapy. Individuals taking other medications known to affect thyroid, hepatic, or renal function were excluded. Written informed consent was acquired from guardians after explaining the study's purpose, methods, potential risks, benefits, and consequences. Ethical approval was granted by the institutional review board of Mymensingh Medical College. Newly diagnosed epileptic patients visiting the pediatric outpatient clinic or admitted to the ward at MMCH were enrolled. Epilepsy diagnosis was based on detailed history and thorough clinical evaluation. Seizure types were classified following the International League Against Epilepsy criteria. Thyroid function was assessed before initiating VPA and again after six months of treatment. Hormone levels were measured using radioimmunoassay kits: FT_3 and FT_4 with Amalex kits (Amerston International) and serum TSH with a kit manufactured in Shanghai, China. Statistical analysis was performed using SPSS version 23.0 for Windows, with data verified twice before analysis Means were computed, and quantitative findings were expressed as frequencies and percentages. A paired t-test was used to compare patient data at baseline and the six-month follow-up. A p-value below 0.05 was regarded as statistically significant.

Results

A total of 80 children with newly diagnosed epilepsy were included in this study. The majority of participants were aged 2-8 years (65%), followed by 5-7 years (22.5%) and >7 years (12.5%) (Table 1). The mean age was 4.81±2.06 years (range: 2-12 years). Regarding sex, males outnumbered females with a ratio of 1.6:1, comprising 49(61.0%) and 31(38.8%) participants, respectively (Table II). The mean weight of the patients was 15.82±3.84 kilograms (range: 7.5-30 kilograms).

Table I: Age distribution of the study patients

Age group (years)	Number of case (n)	Percentage (%)
2-5	52	65.0
5-7	18	22.5
>7	10	12.5
Total	80	100.0

Table II: Sex distribution of the study patients

Sex	Number of casee (n)	Percentage (%)
Male	49	61.3
Female	31	38.8

Among the patients, generalized epilepsy was the most prevalent type, accounting for 58(72.5%) of cases, followed by partial epilepsy 16(20.0%) and unclassified 06(7.5%) (Table III). Before initiating valproate therapy, all patients exhibited normal thyroid function as measured by TSH, FT_3, and FT_4 levels. However, after six months of treatment, significant changes were observed. Serum TSH levels increased significantly, while FT_3 and FT_4

levels decreased. Consequently, 19(23.8%) of patients developed elevated TSH levels exceeding the normal range (0.6-6.3 µIU/ml), indicating potential hypothyroidism. Additionally, 08(10.0%) and 06(7.5%) of patients experienced decreased FT_4 and FT_3 levels, respectively, suggesting subclinical hypothyroidism (Table IV, V, and Figure 1)

Table III: Type of epilepsy in the study patients

Types of epilepsy	Frequency (n)	Percentage (%)
Generalized epilepsy	58	72.5
Partial epilepsy	16	20.0
Unclassified	06	07.5

Table IV: Comparison of FT_3, FT_4, and TSH levels before and 6 months after VPA therapy

Thyroid function test	Duration of therapy		p value
	0 months Mean±SD	6th months Mean±SD	0 months vs. 6 months
FT_3	3.88±0.651	3.290±1.790	<0.006*
FT_4	1.375±0.334	1.109±0.451	<0.001*
TSH	2.723±2.502	5.861±2.367	<0.001*

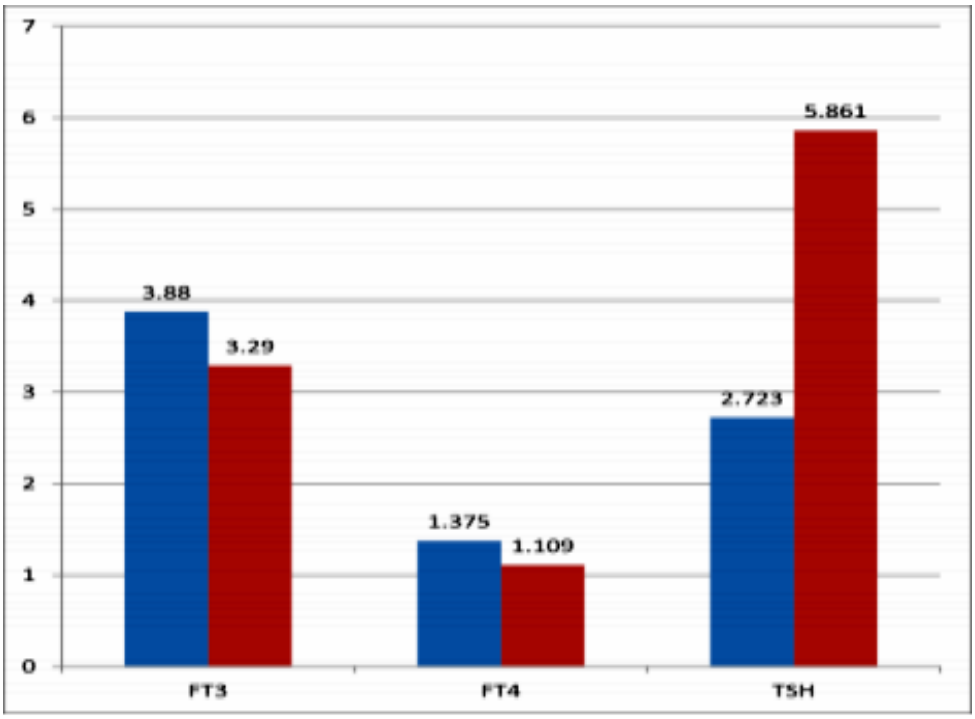

Figure 1: Comparison of thyroid function status of the patients before and 6 months after VPA therapy

Discussion

Antiepileptic medications influence thyroid hormone concentrations through multiple pathways. Several induce hepatic microsomal enzymes, thereby increasing thyroid hormone metabolism; others disrupt hypothalamic-pituitary-thyroid axis regulation. This prospective investigation aimed to evaluate changes in thyroid hormones in pediatric epilepsy patients receiving sodium valproate as single-agent therapy. Eighty newly diagnosed children aged 2-12 years, attending Mymensingh Medical College Hospital,

were enrolled. Baseline thyroid function (FT_3, FT_4, TSH) was measured before starting valproate. Participants were monitored regularly, with thyroid profiles reassessed after six months of monotherapy. Multiple reports indicate a higher prevalence of epilepsy in younger children[22,23]. Our results align, showing that most cases (65.0%) occurred in the 2-5-year age group. Males were more frequently affected than females (ratio 1.6:1), consistent with prior research. Generalized seizures were also more common than focal seizures in this pediatric cohort, matching earlier findings. Our analysis detected a statistically significant rise in TSH levels after six months of valproate monotherapy ($p<0.05$). Serum TSH is regarded as the most dependable indicator of thyroid status in patients on antiepileptic drugs. Elevated TSH was observed in 17 of 80 subjects (23.8%) after six months. The rate of subclinical hypothyroidism here (23.8%) appears lower than that reported in a previous study (52.4%)[25]. The mean TSH level at follow-up increased significantly from baseline (2.723±2.50 mIU/ml vs. 5.86±2.35 mIU/ml; $p<0.01$). This finding concurs with research by Rajak et al., who also reported a significant increase in mean serum TSH after six months of valproate treatment (2.723±2.502 mIU/ml vs. 5.005±1.790 mIU/ml; $p<0.05$)[23]. FT_4 levels also declined significantly after six months of valproate monotherapy, with 10.0% of patients falling below the normal range- a trend consistent with related studies. FT_3 decreased in 7.5% of subjects, a result supported by Attilakos et al.[17]. These outcomes indicate that valproate monotherapy in children can induce early thyroid function changes, underscoring the importance of regular thyroid monitoring in this population. Research by Doneray et al. in children on valproate monotherapy for up to six months similarly found significantly increased TSH and decreased FT_4, aligning with our results. That study also noted significantly reduced serum copper (Cu) levels after six months of therapycompared to controls[27]. This suggests that thyroid alterations during valproate treatment might be linked to lower serum copper, though copper levels were not measured in our study and warrant further investigation.

Limitations

We acknowledge that in this study, the sample size was small and the duration of follow-up was short; thus, the results cannot be generalizable.

Conclusion

This research concludes that pediatric epilepsy patients undergoing valproic acid (VPA) treatment for six months or more are at risk for developing subclinical hypothyroidism. Therefore, performing regular serum thyroid hormone tests in children receivingVPA therapy is recommended.

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