Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.6 (2024). p.469-72; DOI: https://doi.org/10.14238/pi64.6.2024.469-72

Original Article

Treatment duration and dosage of valproic acid and subclinical hypothyroidism incidence in pediatric epilepsy patients

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Abstract

Background Epilepsy is a central nervous system disorder characterized by abnormal electrical activity in the brain. Prolonged administration of valproic acid at therapeutic doses can disrupt thyroid function, leading to subclinical hypothyroidism. This condition is marked by elevated thyroid stimulating hormone (TSH) levels, with normal serum free T4 (FT4) levels.

Objective To investigate for possible associations between valproic acid therapy duration and dosage with the incidence of subclinical hypothyroidism in pediatric epilepsy patients.

Methods This analytical, cross-sectional study included children aged 4 months to 18 years treated at the Pediatric Clinic of RSUD Dr. Zainoel Abidin, Banda Aceh, Aceh, from September to November 2023. Subjects diagnosed with epilepsy and treated with valproic acid for at least 3 months were included in this study and underwent FT4 and TSH examinations.

Results Forty-four children met the study criteria. Subclinical hypothyroidism occurred in 5 (11.4%) subjects during valproic acid therapy. Chi-square analysis revealed no significant association between therapy duration ≥1 year (OR 1.286; 95%CI 0.193 to 8.568; P=1.00) or therapy dose ≥20-40 mg/kg/day (OR 3.429; 95%CI 0.351 to 33.518; P=0.37) with subclinical hypothyroidism incidence.

Conclusion Neither the duration nor the dosage of valproic acid therapy were significantly associated with the incidence of subclinical hypothyroidism in children with epilepsy. **[Paediatr Indones. 2024;64:469-72; DOI: https://doi.org/10.14238/pi64.6.2024.469-72].**

Keywords: *subclinical hypothyroidism; valproic acid; pediatric; epilepsy*

Epilepsy is a neurological disorder characterized by impaired electrical activity in the brain and resulting from various factors such as diverse seizure types, varying severity, distinct etiologies, and management approaches.[1,2] A diagnosis of epilepsy in children is confirmed when two seizures occur within more than 24 hours.[3] Clinical information and an indication of a predisposition to recurrence can be derived from an abnormal electroencephalography (EEG). The long-term use of antiepileptic drugs (AEDs), including valproic acid, phenytoin, carbamazepine, and phenobarbital, poses the risk of subclinical hypothyroid side effects.[4]

In a previous cross-sectional in Saudi Arabia, 80 children with epilepsy were divided into two groups: group 1 received line I AEDs and Group 2 received line II AEDs. The group 1 on traditional AEDs/lini I including valproate, carbamazepine, and phenobarbital, while group 2 on newer AEDs/lini II, including levetiracetam, oxcarbazepine, and topiramate. The prevalence of subclinical

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Submitted December 20, 2023. Accepted November 4, 2024.

hypothyroidism was 20% in epileptic children who received valproic acid, carbamazepine, and phenobarbital.[5] Another cross-sectional study in Beirut, Lebanon, identified risk factors for subclinical hypothyroidism during valproic acid use, including young age, valproic acid polytherapy/monotherapy, and a therapy duration of 6-24 months. Of 143 subjects, 36 (25.2%) had subclinical hypothyroidism.[6] Thus this study was aimed to investigate for possible associations between valproic acid therapy duration and dosage with the incidence of subclinical hypothyroidism in pediatric epilepsy patients.

Methods

This cross-sectional study employed consecutive sampling to select participants from patients treated at the Pediatric Polyclinic of RSUD Dr. Zainoel Abidin Banda Aceh, Aceh, from September 1 to November 30, 2023. Inclusion criteria were pediatric patients aged 4 months to 18 years diagnosed with epilepsy and who had received valproic acid therapy for three months or more. Exclusion criteria were epileptic patients with Hashimoto thyroiditis, Down syndrome, Turner syndrome, OR those with a parental history of hyperthyroid or hypothyroid disorders. This study was approved by from the FK USK/RSUD Dr. Zainoel Abidin Ethics Committee. Data were analyzed using *SPSS® 23* software for the Mann-Whitney, Chi-square, and Fisher's tests. The significance level for was established at $P<0.05$.

Results

From September to November 2023, of the 150 children with epilepsy who visited the Pediatric Polyclinic, 44 met the study criteria. Of these, 54.5% were male, 54.5% had received valproic acid therapy for ≥1 year, and 56.8% consumed a valproic acid dose of ≥20-40 mg/kg/day. Among epileptic children undergoing valproic acid therapy, 11.4% exhibited subclinical hypothyroidism, as detailed in **Table 1**.

The five epileptic children with subclinical hypothyroidism had median FT4 level of 17.53 pmol/L, (range 13.02 to 19.24 pmol/L) and median TSH level was 5.64 μIU/mL (range 5.1 to 6.8 μIU/mL). Mann-Whitney analysis revealed a significant relationship between TSH level and the occurrence of subclinical hypothyroidism ($P<0.05$), as shown in **Table 2**.

Chi-square analysis presented in **Table 3** revealed that the duration of valproic acid therapy ≥1 year had 1.286 times (95%CI 0.193 to 8.568) the likelihood of causing subclinical hypothyroidism. Similarly, the valproic acid therapy dose ≥20-40 mg/kg/day had 3.429 times (95%CI 0.351 to 33.518) the likelihood of causing subclinical hypothyroidism. However, there was no significant association between

Table 1. Characteristics of research subjects

Characteristics	(N=44)
Gender, n (%)	
Male	24 (54.5)
Female	20 (45.5)
Median age, months	103 (10-211)
Therapy duration, n (%)	
<1 year	20 (45.5)
≥1 year	24 (54.5)
Dosage, n (%)	
15-19 mg/kg BW/day	19 (43.2)
≥20-40 mg/kg BW/day	25 (56.8)
Median FT4, pmol/L	17.47 (12.09-100)
Median TSH, μIU/mL	2.46 (0.37-6.8)
Subclinical hypothyroidism	
Yes	5 (11.4)
No	39 (88.6)

BW=body weight

Table 2. Analysis of FT4 and TSH in subjects with and without subclinical hypothyroidism

Variables	Subclinical hypothyroidism (n=5)	Non-subclinical hypothyroidism (n=39)	Significance
Median FT4 , pmol/L	17.53 (13.02-19.24)	17.4 (12.09-100)	Zm-w= -0.906 (P=0.365)
Median TSH, μIU/mL	5.64 (5.1-6.8)	2.24 (0.37-4.68)	Zm-w= -3.606 (P=0.001)

Zm-w= Mann-Whitney test; P<0.05 is significant

Table 3. Analysis of valproic acid therapy duration and dose with occurence of subclinical hypothyroidism

Clinical characteristics	Subclinical hypothyroidism (n=5)	Non-subclinical hypothyroidism (n=39)	OR (95%CI)	P value
Therapy duration, n (%)			1.286	1.00*
<1 year	2	18 (46.2)	(0.193 to 8.568)	
≥1 year	3	21 (53.8)		
Dosage, n (%)			3.429	0.37*
15-19 mg/kg BW/day	1	18 (46.2)	(0.351 to 33.518)	
≥20-40 mg/kg BW/day	4	21 (53.8)		

*Fisher's test

duration nor dose and the occurrence of subclinical hypothyroidism.

Discussion

Long term use of antiepileptic drugs, particularly valproic acid (AED line I), has the potential to disrupt thyroid hormone equilibrium, contributing to conditions such as subclinical hypothyroidism.[7] In our study, 24 of 44 subjects (54.5%) were male. A similar trend was observed in Saudi Arabia case control study in 2020, which had a comparable percentage of males (427/756; 55.7%).[8] Additionally, a study in Seoul reported a higher prevalence of male epilepsy patients using valproic acid (55.7%) compared to females.[9] The incidence of epilepsy tends to be higher in males than females, although variations in study outcomes may arise from differences in subject selection methods.[10] Furthermore, the underreporting of female cases contributes to incomplete data.[11]

The median age of our subjects was 103 months (8.5 years), ranging from 10 to 211 months (17.5 years). A previous study reported a mean subject age of 7.82 years.[12] Subclinical hypothyroidism was identified in 5 subjects (11.4%) in our study. This findings aligned with a study at Adam Malik Hospital, Medan, where the frequency of subclinical hypothyroidism was 7 of 49 subjects (14.3%).[12] A study in Lebanon reported a 25.2% incidence of subclinical hypothyroidism among 143 subjects, which was also consistent with our results.[13]

Three subjects (60%) with a valproic acid therapy duration of ≥ 1 year experienced subclinical hypothyroidism. Chi-square analysis revealed that subjects with a duration of valproic acid therapy ≥1 year had a 1.286 times higher likelihood of developing subclinical hypothyroidism. However, this was not statistically significant (95%CI 0.193 to 8.568; P=1.00). A study in Turkey, using a case-control and prospective design, found 23 of 124 subjects (18.5%) with subclinical hypothyroidism had a mean therapy duration of 16.9 (SD 4.5) months (12-24 months).[14] A study in India reported that 15 of 57 subjects (26.3%) with subclinical hypothyroidism had a median therapy duration of 21 months.[15] Similarly, another study observed a 25.5% incidence of subclinical hypothyroidism in children with a valproic acid therapy duration of 41 (12-108) months.[16]

Four of our 5 subjects with subclinical hypothyroidism (80%) used valproic acid doses of ≥20-40 mg/kg/day. Subjects with such doses had a 3.429 times higher likelihood of developing subclinical hypothyroidism. However, this association was also not statistically significant (95%CI 0.351 to 33.518; P=0.37). These findings aligned with a study which concluded that there was no significant relationship between gender, drug dose, and serum valproic acid levels in subclinical hypothyroidism.[11] This contrasts with a study which suggested that gender, type of epilepsy, and dose of valproic acid could influence subclinical hypothyroidism.[9] The duration of therapy and the dose of valproic acid may impact subclinical hypothyroidism due to valproic acid serum levels. However, the absence of valproic acid serum level measurements in this study poses a limitation. Valproic acid operates by inhibiting GABA receptors, and the mechanism of subclinical hypothyroidism due to valproic acid involves GABA stimulation. This stimulation leads to the inhibition of somatostatin secretion, which acts as a TSH inhibitor. The deficiency of somatostatin causes an increase in TSH production.[7]

The limitation of this study is the small number of the subjects and the absence of data on previous FT4 and TSH values, particularly before initiating

valproic acid therapy. Also, thyroid function tests were conducted only once during valproic acid treatment. Further studies on subclinical hypothyroidism are needed, with a case-control approach to compare normal children and epileptic children receiving valproic acid or epileptic children using valproic acid and other AED groups (monotherapy or polytherapy).

In conclusion, we found no significant associations between the incidence of subclinical hypothyroidism and valproic acid therapy duration and dose.

Conflict of interest

None declared.

Funding acknowledgment

This research was funded by independent sources (private funding).

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