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Original Article

Valproate use and thyroid dysfunction in children with idiopathic epilepsy

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Abstract

Background Long-term administration of valproic acid (VPA) has side effects, including thyroid dysfunction. Subclinical hypothyroidism (SCH) identified by elevated serum thyroid stimulating hormone (TSH) concentrations with normal thyroxine (T4) and triiodothyronine (T3), or normal free thyroxine (fT4) and free triiodothyronine (fT3) has been demonstrated in idiopathic epilepsy patients receiving VPA.

Objective To evaluate for associations between age at initiation of VPA treatment and duration of treatment with thyroid dysfunction.

Methods A cross-sectional study was conducted from October 2012 to May 2013 in Haji Adam Malik and Pirngadi Hospitals, Medan, North Sumatera. Subjects were children ranging from 0 and below 18 years who had been diagnosed with idiopathic epilepsy. Blood specimens were taken to evaluate serum T3, T4, and TSH levels in all subjects. Data were analyzed using bivariate and multivariate analyses.

Results A total of 49 subjects were included in the study. Age of ≤ 4 years at initiation of VPA was found to be a significant risk factor for SCH in the bivariate analysis (OR 6.67; 95%CI 1.215 to 36.594, P=0.036). Three factors had P values <0.25 in the bivariate analysis and were subsequently analyzed by stepwise multivariate regression test: age at initiation of VPA, duration of treatment, and drug dosage. The VPA initiation at age <4 years had 6.67 times the risk of SCH than the age of >4 years (95%CI 1.215 to 36.594; P=0.029). Duration of treatment and VPA dosage were not significantly associated with SCH on multivariate analysis

Conclusion Age ≤ 4 years old at the initiation of VPA is associated with thyroid dysfunction. However, no significant association was found between duration of treatment as well as drug dosage with thyroid dysfunction. **[Paediatr Indones. 2018;58:192-7; doi: http://dx.doi.org/10.14238/pi58.4.2018.192-7]**.

Keywords: *idiopathic epilepsy; thyroid dysfunction; valproic acid; subclinical hypothyroidism*

Epilepsy is a chronic condition characterized by recurrent seizures and occurring with or without stimulation. Epilepsy is common in children, with an incidence of 50 new cases per 100,000 population.[1] Idiopathic epilepsy is genetically determined and has no apparent structural cause.[2] The main treatments for epilepsy are antiepileptic drugs (AEDs), chosen in accordance with the frequency of seizures.[3] Thyroid hormone homeostasis can be impaired by phenytoin, phenobarbital, and carbamazepine, as potent inducers of cytochrome P450 enzymes.[4] In contrast, the mechanism of thyroid dysfunction by valproic acid (VPA) remains unclear.[5,6]

Subclinical hypothyroidism (SCH) is a common side effect of VPA use. A study in India reported that the prevalence of subclinical hypothyroidism in idiopathic epilepsy with VPA monotherapy was 26%.[7] Subclinical hypothyroidism is marked by

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an increase in TSH accompanied by normal free thyroxin (ft4) and free triiodothyronine (ft3), or thyroxine (t4) and triiodothyronine (t3). These circumtances are not always followed by significant clinical manifestations, but should not be ignored, as impaired neurodevelopment leads to defects in cogitive function, particularly in children.[8] Several possible risk factors for thyroid function disorders are the age at initiation of VPA, duration of VPA use, and concomitant use of VPA with other AEDs, like carbamazepine.[9] The aim of our study was to evaluate for possible associations between thyroid dysfunction with age at initiation of VPA and duration of treatment.

Methods

A cross-sectional study was conducted in Haji Adam Malik and Pirngadi Hospitals from October 2012 to May 2013. Inclusion criteria were children diagnosed with idiopathic epilepsy, aged below 18 years, and who received VPA as antiepileptic monotherapy. We excluded children diagnosed with endocrine, heart, renal, or liver disease, those who used drugs known to interfere with thyroid function, and those with family history of hypothyroidism or hyperthyroidism.

History of some clinical manifestation of subclinical hypothyroidism such as short stature, alteration of the school yield, skin dries, fragile hair, and muscle pain was taken from parents and subjects. Body weight (BW) was measured by *Camry®* scales and body height by microtoise. Blood specimens (3 mL) were obtained from the median cubital vein, without anticoagulant, using a 3 mL syringe. Serum thyroid was measured using an automatic *COBAS e601 Roche Diagnostic®* (Swiss) with electrochemistry immunoassay (ECL). Serum thyroid concentration was reevaluated 2 weeks after the first examination in patients suspected to have thyroid dysfunction. Thyroid hormone levels were compared to the reference values from the *Unit Kerja Koordinasi (UKK) Endokrinologi IDAI (Endocrinology Working Group of Indonesian Pediatric Society)*.[10]

Data were processed and analyzed using *SPSS version 15.0* software. Statistical analyses used were Chi-square, Fisher's exact, and Mann-Whitney tests, with significance at $P < 0.05$. All risk variables with $P < 0.25$ in the bivariate analysis were included in the multivariate analysis. Variables were assessed with binary logistic regression with significance value of $P < 0.05$ and 95%CI. Subjects' parents provided written informed consent. This study was approved by the Ethics Committee of the Universitas Sumatera Utara Medical School.

Results

Of 53 children who visited the outpatient clinics, 4 were excluded. Two of these children had consumed drugs that can interfere with thyroid function (ferrous sulphate and mefenamic acid), and the other 2 children had severe disease (dengue shock syndrome and brain injury). Hence, 49 subjects underwent serum thyroid examinations.

Table 1. Subjects' characteristics

Characteristics	(N = 49)
Sex, n (%)	
Male	27 (55.10)
Female	22 (44.90)
Mean height (SD), cm	122.5 (23.80)
Mean weight (SD), kg	28.3(15.41)
Type of epilepsy, n (%)	
Idiopathic general epilepsy	44 (89.80)
Idiopathic partial epilepsy	5 (10.20)
Age at initiation of VPA, n (%)	
≤ 4 years	11(22.40)
> 4 years	38(77.60)
Duration of treatment, n (%)	
< 6 months	5 (10.20)
6-24 months	29 (55.20)
>24 months	15 (30.60)
Mean drug dosage (SD), mg/kg BW	22.3 (3.59)

Mean age at VPA initiation was 7.82 years. The majority of children were >4 years old (77.6%). Most subjects had general idiopathic epilepsy (89.8%). Mean daily dosage of VPA was 22.3 (SD 3.59) mg/kg BW. Most subjects had a 6-to-24-month duration of treatment (55.2%). None of the subjects had below normal height, according to the *Centers for Disease Control and Prevention* (CDC) growth chart for children > 5 years,[11] and the Z-score chart for children ≤ 5 years.[12]

Subclinical hypothyroidism was found in 7/49 (14.3%) subjects (TSH level higher than normal and T3 and T4 within normal limits). In the subclinical hypothyroidism group, mean TSH levels were 6.77 (SD 1.54) μIU/mL in the prepubertal group (age 1 to 10 years old), and 9.29 μIU/mL in the pubertal group (10 to below 18 years, higher than the euthyroid group (mean TSH levels were 2.71 (SD 1.15 in prepubertal group and 2.61 (SD 0.99) in pubertal group. None of the subjects had serum T3 and T4 under and above normal limits.

We evaluated several potential risk factors for subclinical hypothyroidism. Age <4 years at VPA initiation was the only significant risk factor for SCH (P=0.036). Duration of treatment, type of epilepsy, daily VPA dosage, and sex were not significantly associated with SCH (**Table 2**).

Three factors had P values <0.25 in the bivariate analysis: age at VPA initiation, duration of treatment, and VPA dosage. Stepwise multivariate analysis with logistic regression model revealed that VPA initiation at age <4 years had 6.67 times the risk of SCH than the age of >4 years (95%CI 1.215 to 36.594; P=0.029). Duration of treatment and VPA dosage were not significantly associated with SCH on multivariate analysis (**Table 3**).

None of our subjects complained of any clinical manifestation associated with subclinical hypothyroidism, such as short stature, lack of the concentration, dry skin, fragile hair, or muscle pain.

Discussion

In our study, the mean age at VPA initiation was 7 years, with subjects ranging less than 18 years old. Characteristics of our subjects were similar to a 2006 Spanish study of 23 patients who underwent VPA treatment, but they did not specify epilepsy type or neonatal convulsion. It has found an increase of the serum levels of TSH in 7 of 23 patients (30.43%) between 5.85 and 9.24 mUI/L.[13] Our study involved 49 subjects, consisted of only idiopathic epilepsy, and received VPA as AED monotherapy.

Subclinical hypothyroidism was observed in 7 subjects (14.3%). A Lebanese study reported that

Table 2. Bivariate analysis of possible risk factors and subclinical hypothyroidism

Variables	Subclinical hypothyroidism (n=7)	Euthyroid (n=42)	OR	95% CI	P value
Age VPA initiation, n (%)					
≤ 4 years	4 (57.1)	7 (16.7)	4.61	1.22 to 36.6	0.036
> 4 years	3 (42.9)	35 (83.3)	-	-	
Duration of treatment, n (%)					
< 6 months	0	5 (11.9)	1.32	1.07 to 1.62	0.06
6-24 months	7 (100)	22 (52.4)	-	Ref	
> 24 months	0	15 (35.7)	0.76	0.62 to 0.93	
Type of epilepsy, n (%)					
Idiopathic general epilepsy	7(100)	37 (88.1)	0.85	0.75 to 0.97	1.000
Idiopathic partial epilepsy	0	5 (11.9)	-	-	
Mean VPA dosage (SD), mg/kg	24.1 (2.41)	22.0 (3.69)	-	-	0.087
Sex, n (%)					
Male	5 (71.4)	22 (52.4)	2.04	0.44 to 9.50	0.436
Female	2 (28.6)	20 (47.6)	-	-	

Table 3. Multivariate analysis of possible risk factors and subclinical hypothyroidism

Risk factors	Coefficient	Adjusted OR	95% CI	P value
Age at the first VPA use	1.897	6.67	1.215 to 36.594	0.029
Duration of treatment	-1.020	0.304	0.052 to 2.518	0.304
Valproic acid dosage	0.165	1.180	0.900 to 1.546	0.231

25.2% of patients using VPA as an antiepileptic experienced subclinical hypothyroidism compared to control.[14] Another study in India showed a SCH prevalence of 26%.7 In contrast, two studies reported no impaired thyroid function after the use of antiepileptics. An Iranian study concluded that serum thyroid levels were within normal limits after use of phenobarbital, carbamazepine, valproic acid, and primidone for 2 months.[15] Also, an Italian study concluded that VPA monotherapy did not have a significant effect on thyroid disorders.[16]

The lower percentage of patients with subclinical hypothyroidism in our study compared to that of past studies may have been due to different definitions of subclinical hypothyroidism. There are study used VPA only, and some study use some of AED. We used reference values from the *Endocrinology Working Group of Indonesian Pediatric Society*, which differentiates normal serum thyroid based on age. The definition of normal TSH has long been debated and TSH level seems to vary widely in different populations and according to different study methods.[17]

The underlying mechanism of VPA effect on thyroid levels may be due to the γ-aminobutyric acid-stimulating properties of VPA. The γ-aminobutyric acid inhibits the release of somatostatin, which inhibits TSH secretion. A secondary factor is exhibited by zinc and selenium deficiencies result on malfunction of the human 5'deiodinase.[9,14] A longitudinal, controlled study revealed alterations in serum thyroid profiles were associated with low serum copper.[18] We did not evaluate for mineral deficiencies in our subjects, thus, we cannot comment on these potential effects.

Several factors reportedly play a role in causing thyroid dysfunction in patients with epilepsy who use VPA as an antiepileptic drug. An Indian study reported such factors to be the age of the child at VPA initiation, long-term use, and antiepileptic polytherapy use.[7]

We found that age <4 years at VPA initiation was a significant risk factor for SCH, with a 6.67 times increase than in children >4 years old (multivariate analysis: 95%CI 1.215 to 36.594; P=0.029). Previous studies also found that younger age was associated with subclinical hypothyroidism.[9,13,14] Duration of treatment was not a significant factor in our study, as most subjects were in the 6-24-month duration of treatment, and all subjects with SCH were in this group. In contrast, Kim *et al.* reported a higher prevalence of thyroid disorders than in our study.[9] In addition, an Italian study in 2006 found that serum T4, fT4, T3, fT3 and rT3 levels decreased in the third and sixth month while on oxcarbazepine, whereas those using VPA had serum T4, fT4, T3, FT3, and RT3 levels almost equal to the base value, but increased mean serum TSH level, especially after 6 months of use. Those who used oxcarbazepine did not experience a significant change in serum TSH. This finding suggests that thyroid dysfunction may occur after 6 months of VPA use.[19]

A Korean study also assessed several other factors such as serum levels of VPA, phenobarbital and carbamazepine, gender, type of epilepsy, and drug dosage. Among these factors, only serum VPA level was associated with thyroid malfunction.[9] We also conducted an analysis of gender, epilepsy type, and drug dosage, but found no significant associations between these factors and SCH. Measurement of serum VPA levels was not performed on our study due to unavaibillity of facilities.

Subclinical hypothyroidism can lead to clinical symptoms, such as growth failure and cognitive impairment, when the patient falls into a state of overt hypothyroidism. Monitoring of thyroid hormone levels is imperative so that therapy can be administered immediately, especially in high-risk groups, namely under the age of two years.[8] In our study, subjects had no clinical manifestations of hypothyroidism.

Several studies have shown that treatment of subclinical hypothyroidism can reduce the risk of overt hypothyroidism.[20,21] Currently, there is no consensus on management of subclinical hypothyroidism in patients using VPA. Regular monitoring of serum thyroid levels every six months should be performed.[20] For the treatment of subclinical hypothyroidism in patients with manifestations, administration of L-thyroxine can be considered, as it may prevent atherosclerosis and intellectual impairment.[21]

To our knowledge, this study is the first conducted in Indonesia to assess the risk factors for thyroid dysfunction in patients with idiopathic epilepsy using VPA monotherapy as an AED. Moreover, this study focused on the use of VPA as the antiepileptic drug. Our results show that despite relative safety and stability, the use of VPA monotherapy at the age of <four years may increase the risk of thyroid

dysfunction in patients with idiopathic epilepsy.

A limitation in our study was that the baseline TSH level was not measured before VPA treatment started. Also, a more complete examination such as evaluating serum antithyroid antibodies, zinc, copper, and selenium was also not performed due to lack of measurement tools and facilities in Haji Adam Malik Hospital. Another limitation was the broad age range of the subjects, because thyroid dysfunction may have more significant effects on the development of children at younger ages. Indeed, the risk factor for the occurrence of thyroid dysfunction was VPA initiation at <4 years of age. Although there were no clinical manifestations that arose due to subclinical hypothyroidism, VPA use at a younger age should be accompanied by regular monitoring in order to avoid overt hypothyroidism which can cause developmental disorders in children.

In conclusion, age <4 years at valproic acid initiation is significantly associated with thyroid dysfunction. However, no association was found between duration of treatment as well as drug dosage with thyroid dysfunction. Further studies should be done with a larger sample size scale and prospective cohort design.

Conflict of Interest

None declared.

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